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Influence of donor capnometry on renal graft evolution in uncontrolled donation after circulatory death

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Abstract

Aim: To analyse the association between donor capnometry data and the short-term evolution of kidney grafts in cases of uncontrolled donation after circulatory death (uDCD).

Method: We used an ambispective observational study design, conducted in the Community of Madrid between January and December 2019, inclusive. Patients who suffered out-of-hospital cardiac arrest (CA) with no response to advanced cardiopulmonary resuscitation (CPR) were selected as potential donors. Donor capnometry levels were measured at the start, midpoint and transfer to hospital then compared with indicators of renal graft evolution.

Results: The initial selection included 34 possible donors, of which 12 (35.2%) were viable donors from whom 22 (32.3%) kidneys were recovered. There was a correlation between the highest capnometry values and less need for post-transplant dialysis ($\geq$24 mmHg, $p < 0.017$), fewer dialysis sessions and fewer days to recover correct renal function (Rho -0.47, $p < 0.044$). There was a significant inverse correlation between the capnometry values at transfer and 1-month post-transplant creatinine levels (Rho -0.62, $p < 0.033$). There were no significant differences between the capnometry values at transfer and primary nonfunction (PNF) or warm ischaemia time. One-year patient survival was 100% for patient receiving organ donation, while graft survival was 95%.

Conclusions: Capnometry levels at transfer are a useful predictor of the short-term function and viability of kidney transplants from uncontrolled donations after circulatory death.

Keywords: Capnometry, Kidney transplant, Asystole, Resuscitation, Emergency medical services

Introduction

A kidney transplant is the best replacement therapy for patients with end-stage kidney disease.[1] However, the lack of donors limits the treatment's application. In addition, the disparity between the number of patients with chronic kidney disease (CKD) awaiting a kidney transplant and the number of potential donors has increased in recent years following a reduction in the mortality of traumatic head injuries caused by work-related or road traffic accidents.[2,3]

Given this context, uncontrolled donation after circulatory death (uDCD), defined as patients who have died following an unexpected and witnessed cardiac arrest (CA),[4] and unsuccessful cardiopul-

monary resuscitation (CPR). It is particularly important because it is still a significant source of organs, despite the negative impact of the COVID-19 pandemic which paralysed donation procedures in emergency departments.[5]

uDCD protocols are complex programmes and there are currently only a few operating worldwide, mainly in European countries.[6] They start with out-of-hospital treatment, in the street or at the patient's home, and require urgent transfer to hospital via a ground or air ambulance while receiving continuous cardiopulmonary resuscitation.[7] European experts support and encourage the development and optimisation of uDCD programmes, provided that potential donors are identified correctly[8] and they receive high-quality CPR.[9,10]

Based on these criteria, the survival of renal grafts from uDCD donors is no worse than that of kidneys recovered from donation after brain death donors[11] or controlled donation after circulatory death (cDCD) donors.[12] However, organs recovered from uDCD donors endure a lot of ischaemic stress that can compromise their viability. In fact, the percentage of organs rejected for transplant after they have been recovered is significantly higher than for other types of donors. There is also a longer delay until uDCD renal grafts start to function because of severe tubular necrosis, produced by the ischaemic stress during the donation process.[10]

Capnometry is a noninvasive method that measures the partial pressure of expired CO_2, in mmHg, which provides useful information about cell metabolism.[13] It can be used to look at the level of tissue perfusion during the uDCD organ preservation process and throughout the course of the CPR received while being transferred to hospital. Capnometry levels during CPR may be a predictor of renal graft evolution in the donation process.[14]

The new European Resuscitation Council CPR Guidelines indicate the importance of using state-of-the-art devices, e.g., capnography monitors, to measure the quality of the CPR and assess the likelihood of the return of spontaneous circulation (ROSC) if there is a significant increase in ETCO$_2$ values, given that it is an early sign and prognostic indicator of ROSC.[15] Recent studies have underlined the importance of monitoring trends in capnometry levels to detect the possibility of a ROSC and shown that it is a vital tool when evaluating perfusion[16] and selecting organs.[17,18]

Accordingly, we hypothesize that recipients of kidney grafts from uDCD procedures with higher capnometry levels obtain better post-transplant results in terms of renal graft evolution. The aim of this study is to analyse the association between donor capnometry data and the short-term evolution of uDCD kidney grafts.

Method

This study followed an ambispective observational design to look at the association between uDCD donor capnometry levels and the evolution of renal grafts in the first 12 months post-transplant. The data were recollected retrospectively and the recipients were tracked over time.

The study was conducted in the Community of Madrid between January and December 2019, inclusive, at the 12 de Octubre University Hospital, San Carlos University Hospital and the Community of Madrid Out-of-Hospital Emergency Service (SUMMA 112), Fig. 1.

Donors were selected in accordance with the protocols established by the Community of Madrid Regional Transplant Office.

Patients who suffered an out-of-hospital CA with no response to advanced CPR, and who met all the inclusion criteria and none of the exclusion criteria, were selected as potential uDCD donors.

Inclusion criteria: patients aged 16–60 years who suffered a witnessed CA, with an asystolic pattern (regardless of the initial rhythm of the CA), received advanced life support (ALS) within 15 minutes, CPR for at least 20 minutes, and arrived at the hospital within 120 minutes.

Exclusion criteria: exsanguination due to thoracic and/or abdominal lesions, suspected malignancy, infection or intravenous drug use, and chest circumference consistent with the use of a chest compression device.

The following data were collected with respect to donors: age, sex, body mass index, medical history, suspected cause of death reported by the emergency medical service, time of CA, arrival of ALS, ALS arrival at the hospital, time of death, cold and warm ischaemia times for each organ, use of cardiocompressor and capnometry levels. Capnometry values were measured using a Microstream™ Advance FilterLine Set, adult/paediatric, 6.5 ft capnography sampling line placed between the humidifying filter and endotracheal tube (ETT), providing reliable detection and quantification of the intubated patient's expired CO_2. The data were automatically recorded and stored in a LIFEPAK 15 defibrillator/monitor (Physio-Control, Redmond, USA). The data were transferred from the defibrillator/monitor to an ALTECH 1 tablet via a wireless WAN antenna.

Capnometry values were recorded at three time points: Start capnometry was the first value recorded by the emergency medical team after initiating treatment for the CA, once the patient was intubated. Midpoint capnometry was the level recorded at the time halfway between the start value and the measurement taken when the patient was transferred to hospital. Transfer capnometry was the last value measured in the patient's record before being transferred to the hospital bed.

The donor's and recipient's data were gathered from their electronic medical records which were accessed via the Horus system, a software platform for sharing the clinical data of patients of the
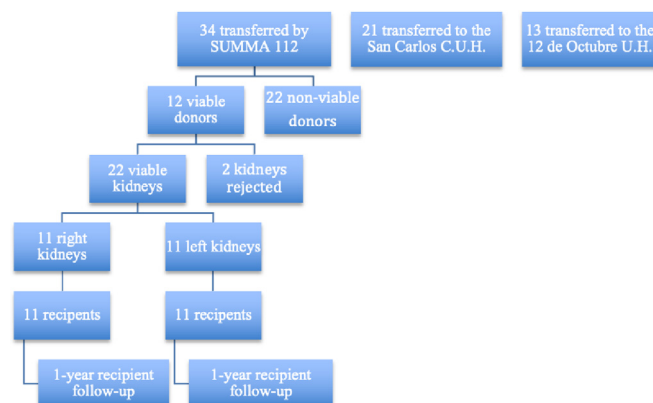

Fig. 1 – Study process flow diagram. uDCD: Uncontrolled donation after circulatory death CAM: Community of Madrid.

Madrid Health Service. Any information that could not be collated from Horus was obtained from records held by the hospitals' Transplant Coordination Offices.

Recipients were patients on haemodialysis and selected from each hospital's kidney transplant waiting list. The following data were collected for recipients: organ transplanted, cause of chronic kidney disease (CKD), dialysis start date, number and types of incompatibilities, kidney failure, acute rejection, number of post-transplant dialysis sessions, primary nonfunction, delayed graft function, urological complications, related infections, creatinine and proteinuria levels at 1, 7, 15, 30, 90, 180 and 360 days post-transplant, 1-year graft and patient survival rates, and death.

The quantitative variables were expressed as the median [interquartile range] and the qualitative variables as absolute (n) and relative frequencies (%). The association between donor capnometry levels (start, midpoint, transfer) and the creatinine and proteinuria values on the various sampling days was examined using Spearman's correlation coefficient. The relationship between the qualitative variables and the capnometry levels was assessed with the Wilcoxon test. We also compared the difference between the start and transfer capnometry values in terms of renal graft evolution, based on the aforementioned concept that a sudden increase in $ETCO_2$ is predictive of a return of spontaneous circulation.[14] Statistical significance for the results was set at a p-value ≤0.05.

The statistical analysis was run using R software, v 4.1.

The study was approved by the Francisco de Vitoria University Research Ethics Committee, number 33/2018, and followed the Declaration of Helsinki guidelines.

Results

Donors

Throughout 2019, data were collected from 34 potential donors comprising 28 men (82.4%) and 6 women (17.6%) with a median age of 48.0 years [44.2–54.2], a median weight of 80.0 kg [75.0–85.0] and a median height of 175 cm [170–178]. Based on their medical histories, 10 donors (29.4%) had hypertension, 1 (2.9%) had diabetes, 13 (38.2%) were smokers and 8 (23.5%) had hypercholesterolaemia (Table 1).

The main cause of death was arrhythmia (14, 41.2%), followed by ischaemic cardiomyopathy (11, 32.4%), unknown causes (4, 11.8%), pulmonary thromboembolism (3, 8.8%) and multiple trauma (2, 5.9%).

Twenty-one donors (61.8%) were transferred to the San Carlos University Hospital and 13 (38.2%) to the 12 de Octubre University Hospital – two (5.8%) of the latter group were transferred in an air ambulance. The emergency medical team used a mechanical chest compression device while transferring 26 donors (76.5%) to hospital and manual compressions for the other 8 donors (23.5%). At the hospital, all donors received continuous mechanical compression with a LUCAS 2 (31, 91.1%) or LUCAS 3 (3, 9.9%) device.

Of the 34 potential donors, only 12 were viable, from whom 22 kidneys (64.7%) were recovered and ultimately transplanted. Two viable livers and two lungs were also recovered. The reasons for rejecting organ donation were poor perfusion (12, 54.5%), dissecting aneurysm (2, 9.1%), vascular malformation (2, 9.1%), infectious process (2, 9.1%), renal thrombosis (1, 4.5%), ischaemia time (1, 4.5%), atheroma (1, 4.5%) and macroscopic appearance (1, 4.5%). The viability of graft evolution was performed by macroscopic assessment

by the surgeon and by pre-transplant biopsy, using capnometry values as a tool to facilitate decision but not to rule out renal grafts. The median warm ischaemia time (WIT), that is, the time between the CA and the start of organ preservation procedures, for all donors was 134 minutes [120–148], while the median WIT for the subgroup of viable donors was 126 minutes [119–148].

Recipients

The recipients had a median age of 51.5 years [43.0–57.8]. Fifteen kidneys (68.2%) were transplanted at the San Carlos University Hospital and 7 (31.8%) at the 12 de Octubre University Hospital. There were two recipients with incomplete data.

Primary nonfunction (PNF), defined as the renal graft's failure to function post-transplant, only occurred in 1 patient (5%).

Delayed graft function, defined as the need for dialysis in the first week post-transplant, was observed in 11 recipients (55%), and the median time required to recover dialysis-free renal function was 11 days [5–18].

One-year patient survival was 100% (22/22) and the graft survival rate was 95% (21/22).

The median creatinine level was 3.43 mg/dL [2.21–5.58] at 1 month post-transplant and 1.76 mg/dL [1.48–2.98] at 6 months. The median proteinuria value was 0.14 mg/dL at both 6 months [0.09–0.19] and 12 months [0.09–0.20].

As for complications, 12 recipients (45%) experienced urological complications and 14 (63.3%) developed infections.

Donor capnometry

To assess the association between the donor capnometry values and renal graft evolution, we collated the capnometry measurements taken while the emergency medical team treated the patient. At the start of the CA, the potential donors had a median capnometry level of 17.0 mmHg [12.0–31.5], at the midpoint it was 25.5 mmHg [17.8–34.2] and for the transfer to hospital it was 22.0 mmHg [15.5–27.5]. Considering the subgroup of viable donors whose organs were transplanted, the median start capnometry was 19.0 mmHg [12.0–35.0], the midpoint value was 22.0 mmHg [17.0–35.0] and at transfer it was 22.0 mmHg [17.0–26.0] (Table 2).

We observed a significant difference between the start capnometry values of potential donors who required manual CPR 32.0 mmHg [24.0–40.0] and mechanical CPR 18.2 mmHg [11.8–23.5] (p-value: 0.049). However, midpoint capnometry values did not differ between manual CPR 34.0 mmHg [24.5–43.5] and mechanical CPR 23.0 mmHg [18.0–32.0] (p-value: 0.232) and there were no significant differences between transfer capnometry values of manual CRP 21.0 mmHg [18.0–32.0] and mechanical CPR 22.0 mmHg [14.0–26.8] (p-value: 0.698). We did not observed significant differences between mechanical CPR and good organ perfusion (p-value: 0.121).

The median cold ischaemia time for the viable donor subgroup, the time between clamping each kidney for removal to when it achieved reperfusion in the recipient, was 16.3 hours [13.0–18.3].

Renal graft evolution

We defined the short-term evolution of the renal grafts according to the following variables: primary nonfunction, delayed graft function, need for post-transplant dialysis, number of post-transplant dialysis sessions, recovery of renal function based on 1-month, 3-month, 6-month and 1-year serum creatinine values, urological complications and related infections.

Table 1 – General donor data, 34 total patients.

	Total
Hospital	
San Carlos Hospital	21 (61.8%)
12 de Octubre Hospital	13 (38.2%)
Age	
Mean ± SD	46.9 ± 10.0
Median [25–75%]	48.0 [44.2–54.2]
Sex	
Male	28 (82.4%)
Female	6 (17.6%)
Weight	
Mean ± SD	82.0 ± 9.5
Median [25–75%]	80.0 [75.0–85.0]
Height	
Mean ± SD	173.8 ± 8.5
Median [25–75%]	175.0 [170.0–178.0]
Blood group	
A	15 (44.1%)
0	13 (38.2%)
B	4 (11.8%)
AB	2 (5.9%)
HTN	10 (29.4%)
Diabetes	1 (2.9%)
Smoker	13 (38.2%)
Cholesterol	8 (23.5%)

Mean ± SD; Median [IQR]; n (%).

The incidence of primary nonfunction (PNF) was 5%. There were no significant differences between the transfer capnometry levels of patient with PNF and those whose grafts evolved favourably (p-value: 0.64). The donor of this renal graft presented a transfer capnometry of 20 mmHg, WIT of 125 minutes and cold ischaemia of 870 minutes. The main complication of the recipient was a renal infarction, which was the reason for PNF.

We observed a significant difference between the transfer capnometry values of patients who required, 17.0 mmHg [15.0–22.0], and did not require post-transplant dialysis, 24.0 mmHg [22.0–29.0] (p-value: 0.017). The difference between the transfer and start capnometry levels (DTSC), which examines the trend in capnometry during the CA, was also statistically significant when comparing the same groups (p-value: 0.046). The WIT did not differ between the recipients who required, 125.0 minutes [116.0–146.0], and did not require dialysis, 142.0 minutes [120.0–151.0] (p-value: 0.32) (Table 3).

There was also a moderate, but significant, negative correlation between the number of dialysis sessions and the transfer capnometry levels, with a Rho value of −0.47. We did not find any significant correlations between any of the other variables studied.

After recovering renal function, there was a significant, inverse correlation between transfer capnometry and DTSC levels and the 15 day and 1 month serum creatinine values. The Rho values for these correlations were 0.57 and −0.62 for the transfer and −0.65 and −0.37 for the DTSC, for 15-day and 1-month creatinine respectively (Table 4).

Discussion

In clinical practice, capnometry is used to assess the return of spontaneous circulation after a CA[15] and it is expected to predict organ perfusion. Therefore, ETCO2 higher during CPR is correlated with better survival and neurological outcome in out of hospital CA.[16,19] In the context of uDCD, this study shows that capnometry is also a useful predictor of the short-term evolution of kidney grafts recovered from uDCD donors.

Table 2 – Comparison of capnometry values of viable and non-viable donors.

	Viable donor			
	Overall, N = 34	No, N = 22	Yes, N = 12	p-value
Start capnometry				0.693
N	27	16	11	
Mean ± SD	21.3 ± 12.0	20.4 ± 11.7	22.6 ± 12.9	
Median [25–75%]	17.0 [12.0–31.5]	17.0 [12.5–31.0]	19.0 [12.0–35.0]	
Midpoint capnometry				0.572
N	28	17	11	
Mean ± SD	27.4 ± 12.2	28.6 ± 13.4	25.5 ± 10.5	
Median [25–75%]	25.5 [17.8–34.2]	29.0 [20.0–34.0]	22.0 [17.5–33.5]	
Transfer capnometry				0.711
N	27	16	11	
Mean ± SD	23.0 ± 11.7	23.7 ± 14.3	21.9 ± 6.8	
Median [25–75%]	22.0 [15.5–27.5]	24.0 [10.8–31.0]	22.0 [18.5–24.0]	
Difference between transfer and start capnometry				0.489
N	27	16	11	
Mean ± SD	1.6 ± 15.1	3.2 ± 15.6	−0.7 ± 14.6	
Median [25–75%]	5.0 [−4.5 to 13.5]	5.5 [−3.2 to 14.2]	3.0 [−11.0 to 11.0]	
Warm ischaemia time (min)				0.626
N	34	22	12	
Mean ± SD	134.3 ± 20.6	135.8 ± 22.5	131.4 ± 17.2	
Median [25–75%]	134.0 [120.0–148.0]	135.0 [120.8–148.0]	125.5 [118.2–144.0]	

Mean ± SD; Median [IQR].
Wilcoxon rank sum test.

Recipients who experienced delayed graft function tended to receive their kidneys from donors with significantly lower transfer capnometry and DTSC values than those recipients who achieved immediate renal function. Similarly, recipients with delayed graft function presented a statistically significant association between higher transfer capnometry and DTSC levels and fewer post-transplant dialysis sessions and fewer days to recover correct renal function. There was a positive correlation between the transfer capnometry and DTSC values and the 1-month serum creatinine levels, whereby the kidney donors with the highest capnometry values corresponded to the lowest post-transplant creatinine levels.

Our data therefore suggest that capnometry levels at transfer and the trend in the DTSC are useful predictors of the short-term function of kidney transplants from uDCD donors. However, start and mid-term capnometry values were not useful predictor for the short-term function of the renal grafts.

This study indicates that kidneys transplanted from donors with lower transfer capnometry and DTSC levels suffered more ischaemic damage, which translated into a greater delay in graft function, requiring more dialysis sessions and more days to recover dialysis-free renal function, and poorer function at 1-month post-transplant based on higher serum creatinine values.

Delayed graft function and short-term graft evolution have been assessed in terms of a range of different variables, including donor age, haemodynamic stability, donor type (living, brain death or cardiac death donation), warm ischaemia time, cold ischaemia time, recipient's immunisation status, vascular anastomosis time, and so on.

To the best of our knowledge, this is the first study to correlate delayed graft function with capnometry levels for kidneys transplanted from uDCD donors. Our findings also suggest that donors who received better cardiac massage, resulting in better tissue per-fusion and higher capnometry levels, suffered less ischaemic stress and presented better recovery of graft function, which is consistent with previous studies.[4]

We did not observe any relationship between warm ischaemia time and delayed graft function, the need for post-transplant dialysis or serum creatinine levels. This agrees with previous studies which found that WIT neither affects the total number of viable donors nor the outcome of kidney transplants, provided that it is within certain limits established by guidelines.[20]

The differences in capnometry values did not bare any influence on the 1-year creatinine and proteinuria levels, which suggests that donors with lower capnometry levels suffered more ischaemic damage. Furthermore, considering the range of capnometry values of all the donors whose kidneys were ultimately transplanted, the incidence of PNF was very low. In this context, establishing a range of capnometry levels that are indicative of irreversible ischaemic damage to a donor's organs would be a useful tool in helping exclude them from donation.

Our data show that uDCD program can be performed with relative safety if midpoint and transfer capnometry levels are above 18 and 19 mmHg, respectively. Notwithstanding, some authors advocate transfer capnometry values of between 23 and 30 mmHg.[17] In a preliminary study, we observed a potential relationship between capnometry values and organ viability, although we could not reach any significant conclusions due to the limited sample size.[18] Further studies are required to determine the lower limit of capnometry levels that can be used to rule out uDCD donors suspected of having irreversible ischaemic damage.

This work is of practical value in various applications for out-of-hospital emergency medical services and transplant coordination offices. Midpoint and transfer capnometry data can help guide donor selection in situations that require the emergency services team to

Table 3 – Relationship between capnometry levels and the need for post-transplant dialysis.

	Need for post-transplant dialysis			
	Overall, $N = 20$	No dialysis required, $N = 9$	Dialysis required, $N = 11$	p-value
Start capnometry				0.478
N	19	8	11	
Mean ± SD	22.9 ± 12.3	19.8 ± 8.7	25.2 ± 14.4	
Median [25–75%]	19.0 [12.0–35.0]	19.0 [15.0–25.0]	35.0 [12.0–37.5]	
Midpoint capnometry				0.261
N	19	8	11	
Mean ± SD	25.7 ± 10.7	22.2 ± 8.5	28.3 ± 11.8	
Median [25–75%]	22.0 [17.5–35.0]	20.0 [16.2–26.0]	23.0 [20.0–38.0]	
Transfer capnometry				0.017
N	19	8	11	
Mean ± SD	22.1 ± 7.2	26.9 ± 7.1	18.5 ± 5.0	
Median [25–75%]	22.0 [17.0–26.0]	24.0 [22.0–29.0]	17.0 [15.0–22.0]	
Difference between transfer and start capnometry				0.046
N	19	8	11	
Mean ± SD	−0.8 ± 14.2	7.1 ± 8.1	−6.6 ± 15.1	
Median [25–75%]	3.0 [−11.0 to 11.0]	9.5 [3.0–13.2]	−9.0 [−16.5 to 6.0]	
Warm ischaemia time (min)				0.32
N	20	9	11	
Mean ± SD	133.3 ± 17.8	136.6 ± 16.7	130.7 ± 19.0	
Median [25–75%]	134.0 [118.2–150.0]	142.0 [120.0–151.0]	125.0 [116.0–146.0]	

Mean ± SD; Median [IQR].
Wilcoxon rank sum test.

Table 4 – Correlation between capnometry values and creatinine and proteinuria levels.
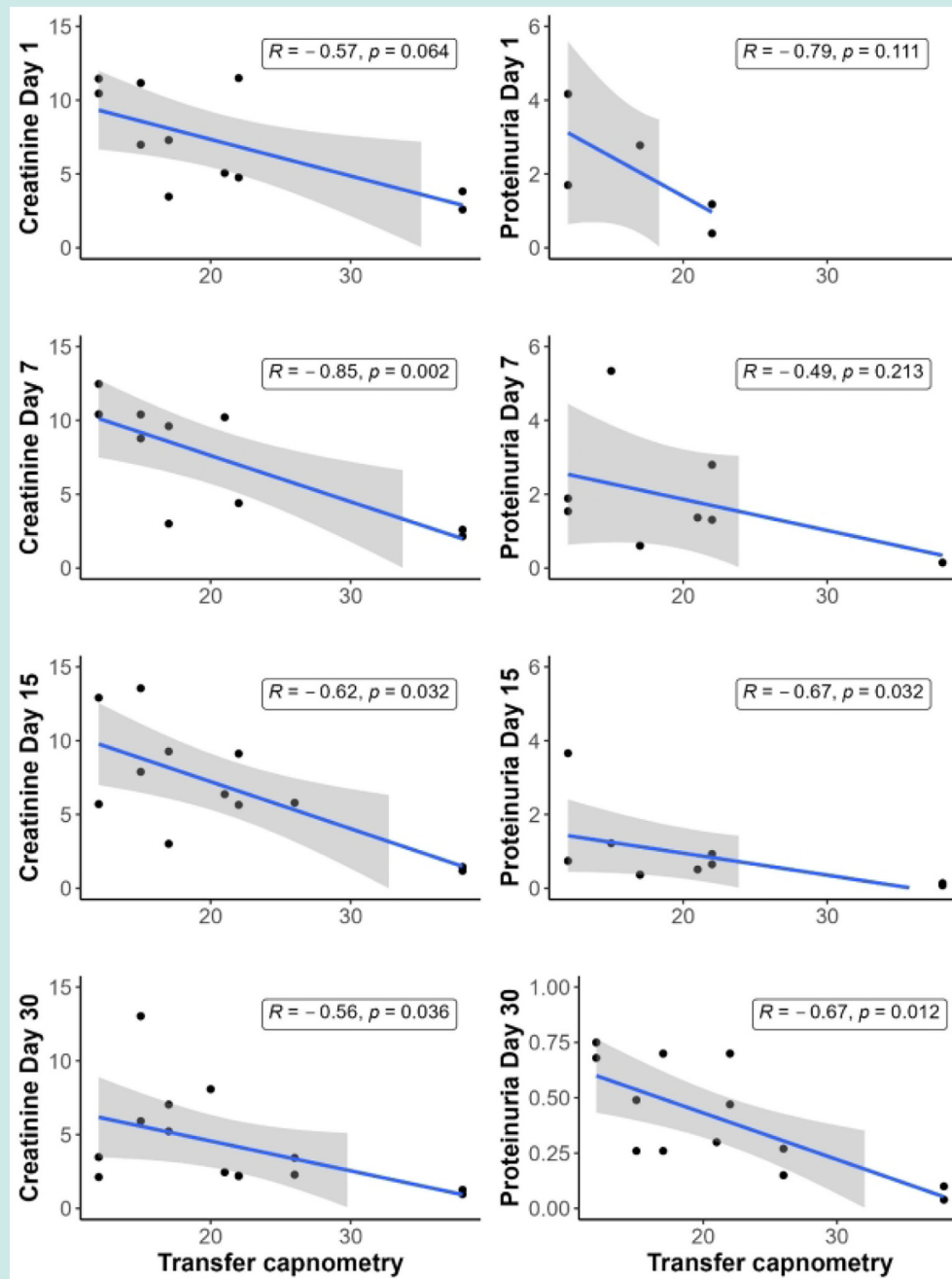
make a complicated decision quickly. Our findings also suggest there is more flexibility when accepting donors, because they support lower (18 mmHg) midpoint capnometry values than usual, thus increasing the number of potential donors.

Nevertheless, the study was not without certain limitations. The main constraint was the small sample size, which was due to the inclusion and exclusion criteria for potential donors. While treating some cases of CA, the healthcare professionals did not record the capnometry levels or some data for other variables, complicating the subsequent statistical analysis.

In conclusion, capnometry levels are a useful predictor of the short-term evolution of kidney transplants from uDCD donors and can help determine organ viability by ruling out uDCD kidneys with irreversible tissue damage.

CRediT authorship contribution statement

Carlos Rubio-Chacón: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Alonso Mateos-Rodríguez:** Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis. **Fernando Neria-Serrano:** Visualization, Software, Methodology, Data curation. **Francisco Del Rio-Gallegos:** Validation, Supervision, Investigation. **Amado Andrés-Belmonte:** Writing – original draft, Supervision, Investigation, Conceptualization.

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.

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