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Time to Cardiac Death After Withdrawal of Life-Sustaining Treatment in Potential Organ Donors

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Organ donation after cardiac death (DCD) is increasing markedly, allowing more patients to benefit from transplantation. The time to cardiac death following withdrawal of life-supporting treatment varies widely and is an important determinant of whether organ donation occurs. A prospective multicenter study of potential DCD donors was undertaken to evaluate the time to death and identify associated factors. One hundred and ninety-one potential adult DCD donors at nine UK centers were studied. Treatment withdrawal comprised stopping ventilator support and inotropes. Demographics and physiological variables at the time of death were recorded. Following treatment withdrawal, all potential donors died, with median time to death of 36 min (range 5 min to 3.3 days). Eighty-three potential donors (43.5%) remained alive 1 h after treatment withdrawal, and 69 (36.1%) and 54 (28.3%) at 2 and 4 h, respectively. Univariate analysis revealed that age, cause of death, ventilation mode, inotrope use, systolic blood pressure, FiO_2 and arterial pH at treatment withdrawal were all associated with time to death. Multivariable analysis showed that younger age, higher FiO_2 and mode of ventilation were independently associated with shorter time to death. This information may aid planning and resourcing of DCD organ recovery and help maximize DCD donor numbers.

Key words: Cardiac death donors, death, deceased donor, donor selection, kidney transplantation, liver transplantation

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Introduction

The demand for organ transplantation far exceeds the number of available donor organs and in the UK, as in many other countries, much effort is being made to increase the number of deceased organ donors. While most deceased donors are heart-beating donors who are certified by brainstem criteria, donation after cardiac death (DCD) has become an increasingly important source of deceased donor organs for transplantation (1). In the UK in 2007, 23% of deceased organ donors were DCD donors, a figure that has risen substantially over the last 5 years from under 7% in 2002 (2). The vast majority of DCD donors in the UK are controlled donors (3) and have usually suffered massive irreversible neurological injury such that the clinicians caring for the patient have concluded that further medical intervention would be futile. In those patients where death cannot be declared by neurological criteria, life-supporting treatment is withdrawn on the intensive care unit or ward following which cardiorespiratory arrest occurs. Following certification of death a period of at least 5 min must have elapsed before surgery could begin. Where appropriate consent has been obtained for organ donation, the deceased person is then transferred promptly to the operating theatre, and organ recovery is performed as soon as possible to minimize warm ischaemic injury. UK legislation does not allow medical interventions that are not in the patient's interest before death is diagnosed, including interventions to facilitate organ donation such as heparinization and vascular cannulation. This contrasts with current practice in the United States.

Following withdrawal of life-supporting treatment in potential DCD donors, the time to death is highly variable, ranging from minutes to hours or sometimes days. The period of time from withdrawal of treatment to death (designated the agonal period, also known as the withdrawal phase in the United States (4)) has an important influence on whether organ donation occurs but is very difficult to predict.

This inability to predict the duration of the agonal period poses two challenges to the transplant team in planning organ recovery. First, a sustained period of hypotension may result in severe organ ischemia that precludes their use for transplantation. Secondly, a lengthy delay between treatment withdrawal and death has important logistical consequences, including indefinite reservation of an operating

theatre, surgical staff on stand by and unavailable for other duties, and transport delays.

There is very little published information on the duration of the agonal phase following withdrawal of life-supporting treatment in potential DCD donors, or how this relates to organ recovery. The ability to predict the likely duration of the agonal period would allow better identification of patients suitable for DCD and facilitate planning of organ recovery. We undertook a comprehensive prospective multicenter study of potential DCD donors to identify clinical parameters that predict the timing of death following treatment withdrawal.

Methods

The study setting

This multicenter study was conducted over a 39-month period between April 2004 and July 2007. Nine of the 11 renal transplant centers in the UK with an active DCD donor programme agreed to participate in the study. The decision to withdraw life-supporting treatment in all cases was made by the intensivist responsible for the patient's care following a decision that continued treatment was futile and was independent of the transplant team. Treatment withdrawal comprised disconnection from the ventilator or extubation, together with simultaneous cessation of all inotropes.

Inclusion and exclusion criteria

The study group comprised all potential DCD donors between 16 and 65 years of age at the participating centers for whom a decision to withdraw treatment had been made. Potential DCD donors were included in the study irrespective of whether organ donation subsequently took place.

Patients were excluded from the study if they had a prior medical contraindication to organ donation such as Human Immunodeficiency Virus (HIV) infection, suspected new-variant Creutzfeld-Jacob disease (nvCJD) and untreated major sepsis. Patients were excluded if they were not intubated, or if the manner of withdrawal of treatment differed from the protocol mentioned above. Patients were also excluded if brain stem death had been certified but then ventilation was discontinued on the intensive care unit at the relatives' request.

Data collection

The local transplant coordinator collected the donor data by completion of a study proforma at the time of or immediately following death. This proforma recorded the following information: age; gender; cause of death; whether apnoea was tested prior to treatment withdrawal; whether withdrawal of ventilatory support was by extubation or disconnection from the ventilator, and time of death following withdrawal of treatment. In addition, immediately prior to treatment withdrawal, the following variables were recorded on the proforma: vital signs; respiratory settings (both spontaneous and/or mandatory); inotropic support; desaturation on tracheal suction and arterial blood gas concentrations.

Transplant outcome data were obtained from the national registry held at NHS Blood and Transplant (formerly UK Transplant). Where donation occurred organ recovery was performed by senior surgeons; where the liver was retrieved this was usually performed by consultant surgical staff.

Before commencing the study, approval was gained from a UK Multicentre Research Ethics Committee.

Statistical methods

Time to death was defined as the period from withdrawal of life-supporting treatment to the point when death was certified following cardiorespiratory arrest. Following certification, there was a period of asystole of at least 5 min before surgery could begin. Kaplan–Meier estimation of the survivor function was performed and subgroups compared using a log-rank test. Continuous measurements were grouped, either according to the normal range for the measurement, or according to a convenient value that allowed a reasonable number of observations in each of the groups. Cox proportional hazards regression was used to assess the effect of measurements on time to death and to build a multiple variable model. Initially, all measurements were assessed individually for inclusion in the model. Forward selection based on the likelihood ratio statistic was used to assess which combination of measurements should be included in the multiple variable model. The final model was confirmed using backward selection.

Data collection was incomplete for 46 cases, the most common omission being blood gas data. In such cases that measurement was excluded from the analysis.

Results

Patient demographics

During the 39-month study period, a total of 191 potential DCD donors were entered into the study. There were 116 (60.7%) males and 75 (39.3%) females and the mean age at death was 44 years (range 16–65). In all cases, death was attributable to severe neurological injury, the most common conditions being intracranial hemorrhage (41.4%), neurotrauma (28.3%) and hypoxic brain damage (15.7%). Other diagnoses included cerebral infarction, cerebral edema, intracranial tumor or abscess, hydrocephalus, neurosurgical complications and liver failure.

Following death, 99 of the 191 potential donors (51.6%) became organ donors, of whom 15 (15.2%) had a time to death after withdrawal of life-supporting treatment of over 60 min.

Withdrawal of life-supporting treatment

Withdrawal of respiratory support was by extubation in 151 patients (79.1%) and disconnection from the ventilator with the endotracheal tube or tracheostomy remaining *in situ* in 40 patients (20.9%). Fifteen patients (7.9%) had undergone apnoea testing prior to withdrawal of treatment as part of the Wisconsin evaluation tool (5).

Time to death

All patients died following treatment withdrawal. The time to death ranged from 5 min to 3.3 days (4779 min) (Figure 1). Most patients died soon after treatment withdrawal, with a median time to death of 36 min. The proportions of patients still alive at 1, 2, 3, 4 and 12 h were 43.5%, 36.1%, 30.9%, 28.3% and 14.1%, respectively. Fewer than 10% remained alive for more than 24 h following treatment withdrawal.

The association between discrete factors and time to death was explored using Kaplan–Meier plots and log-rank

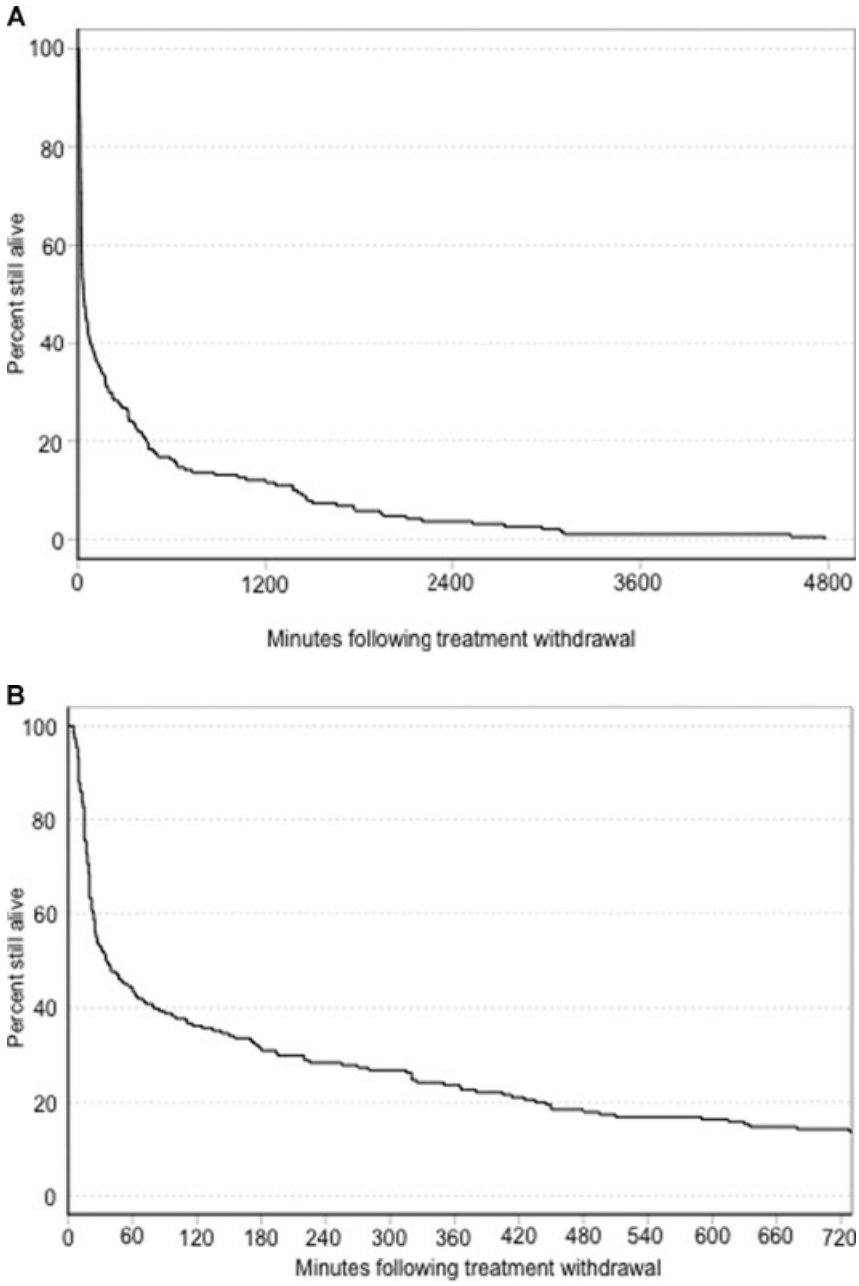


Figure 1: (A) Kaplan–Meier plot showing the time to death from withdrawal of treatment. (B) Details of the deaths in the first 12 h.

statistics. There was no difference in time to death for males and females ($p = 0.874$), nor between patients who had low oxygen saturation ($\leq$95%) and those who had normal oxygen saturation prior to treatment withdrawal ($p = 0.662$).

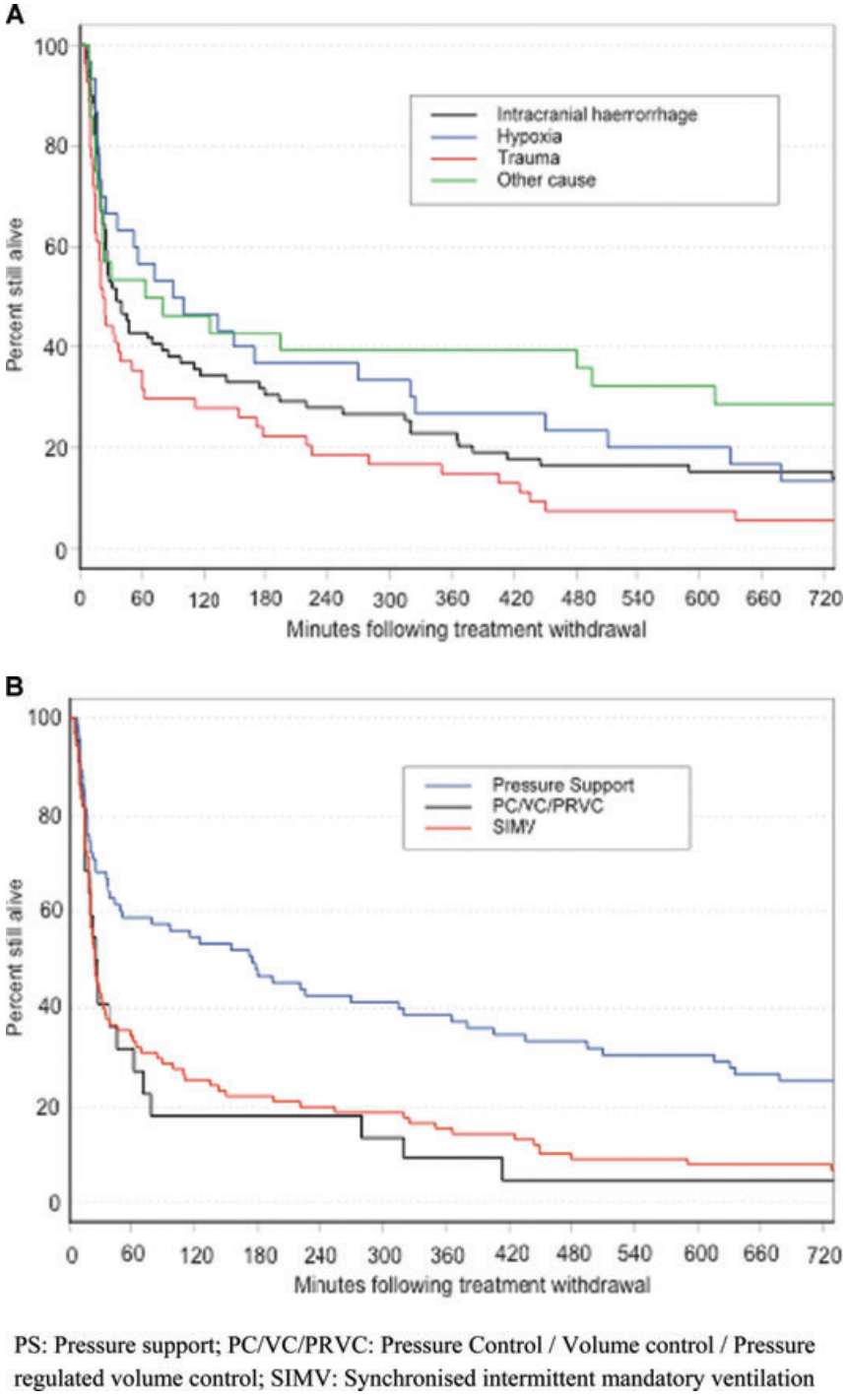
A number of factors were identified that influenced the time to death. There were significant differences in time to death according to the cause of neurological injury ($p = 0.017$, Figure 2A), with those dying as a consequence of intracranial trauma dying most rapidly, followed by those suffering from intracranial hemorrhage and hypoxia; patients dying from causes other than these tended to die more slowly. Patients who were ventilated without pressure support at the time of treatment withdrawal had a shorter time to death than those on pressure support when treatment was withdrawn ($p < 0.001$, Figure 2B). Seventy-three (38%) patients were on inotropes prior to treatment withdrawal, and this was associated with a significantly shorter time to death ($p < 0.001$, Figure 2C).

Using the log-rank test for suitably grouped measurements, the factors at the time of treatment withdrawal that were associated with a shorter time to death included

younger age ($p = 0.002$), high FiO_2 (>50% compared to ≤50%, $p = 0.003$) and lower pH (pH < 7.45 compared to 7.35–7.45 and >7.35, $p = 0.007$). Factors which did not affect the time to death were systolic blood pressure ($p = 0.224$), diastolic blood pressure ($p = 0.443$), oxygen de-saturation ($p = 0.414$), heart rate ($p = 0.416$), PaO_2 ($p = 0.818$), base excess ($p = 0.448$) and the ratio of PaO_2/FiO_2 ($p = 0.252$).

Cox proportional hazards regression analysis of variables affecting the time to death

Initial Cox regression analysis considered each factor individually (Table 1) and, as suggested by the initial analysis, showed that cause of death, mode of ventilation, inotrope use, age, FiO_2 and pH were associated with time to death. Although univariate analysis suggested that a decrease in systolic blood pressure was associated with more rapid



PS: Pressure support; PC/VC/PRVC: Pressure Control / Volume control / Pressure regulated volume control; SIMV: Synchronised intermittent mandatory ventilation

Figure 2: Kaplan-Meier plots showing the effects of different factors on the time to death. (A) Shows the effect of different causes of death, with neurotrauma being associated with the shortest time to death (log rank $p = 0.017$). (B) Shows that the mode of ventilation affects the time to death, with pressure support being associated with a slow deterioration ($p < 0.001$). (C) Shows that the requirement for inotropes at the time of treatment withdrawal is also associated with a faster decline ($p < 0.001$).

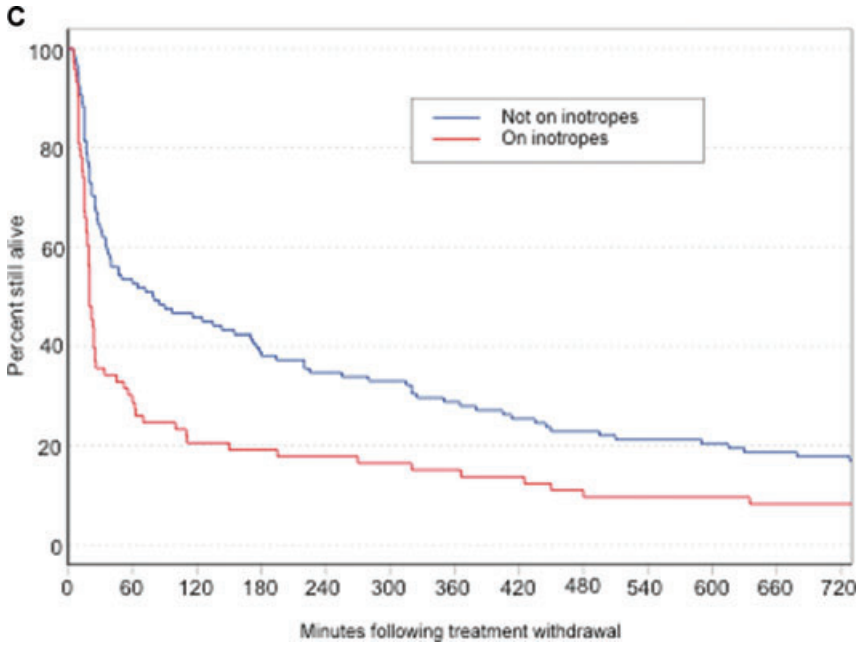


Figure 2: Continued.

death, this association was not seen in the Kaplan–Meier analysis. The effect of patient age on time to death appeared not to be linear and so this was included as a four-level factor (≤30, 31–40, 41–50, >50). All other continuous measurements were considered as linear effects.

Results from the multi-variable model are shown in Table 2. Shorter time to death following withdrawal of treatment was most strongly associated with younger age, higher FiO_2 and mode of ventilation.

Transplant outcomes

Ninety-nine donors provided 217 organs for transplantation: 180 kidneys were transplanted (including 2 kidneys transplanted as a double kidney transplant), 174 solitary kidney transplants and 4 combined with the pancreas; there were also 2 isolated pancreas transplants and 31 liver transplants. All the isolated pancreas and kidney pancreas transplants were still functioning at last follow-up (88 and 360 days for isolated pancreas, 321 to 1129 days for kidney pancreas transplants).

Six of the 31 liver transplants were from donors who died over 30 min after withdrawal of treatment, with one being removed over 23 h following withdrawal of treatment. The 1-year survival of all DCD donor liver transplants was 79.5%; for those donors dying within 30 min, the 1-year liver graft survival was 83.4% compared to 66.7% for donors dying after 30 min ($p = 0.493$) (Figure 3B).

The overall 1-year graft survival for transplanted kidneys was 94.3%. Of the 25 kidneys that were transplanted from donors dying after 60 min (range 63–1428 min), 3 were lost within a week (12%); the 1-year graft survival was 88.0%, compared to 95.4% for kidneys from donors dying within 60 min ($p = 0.170$) (Figure 3A).

Discussion

In the UK, as in other countries throughout the world, DCD donors are an increasingly important source of kidneys, and more recently livers, pancreases and lungs, for transplantation, and may provide transplant outcomes broadly comparable to those for organs from heart-beating deceased donors (6–9). Many patients identified as potential DCD donors do not, however, become organ donors because of a prolonged time to death following withdrawal of life-supporting treatment which may either result in severe ischaemic injury to the organs or make organ recovery logistically impracticable. The results of the present study highlight the great variability in time to death following withdrawal of life-supporting treatment in prospective DCD organ donors. The variability ranged from 5 min to 3.3 days, although two-thirds of the potential donors studied died within 2 h, and three-quarters within 4 h of treatment withdrawal. Our results highlight the fact that many potential DCD donors do not become organ donors and that most of those who do become donors died within the first hour following withdrawal of life-supporting treatment (83% in this study). We identified younger age, higher FiO_2 and mode of ventilation as the most important variables associated with shorter time to death following withdrawal of life-supporting treatment.

The manner in which life-supporting treatment is withdrawn from potential DCD donors varies widely between centers and from country to country. In this report, we

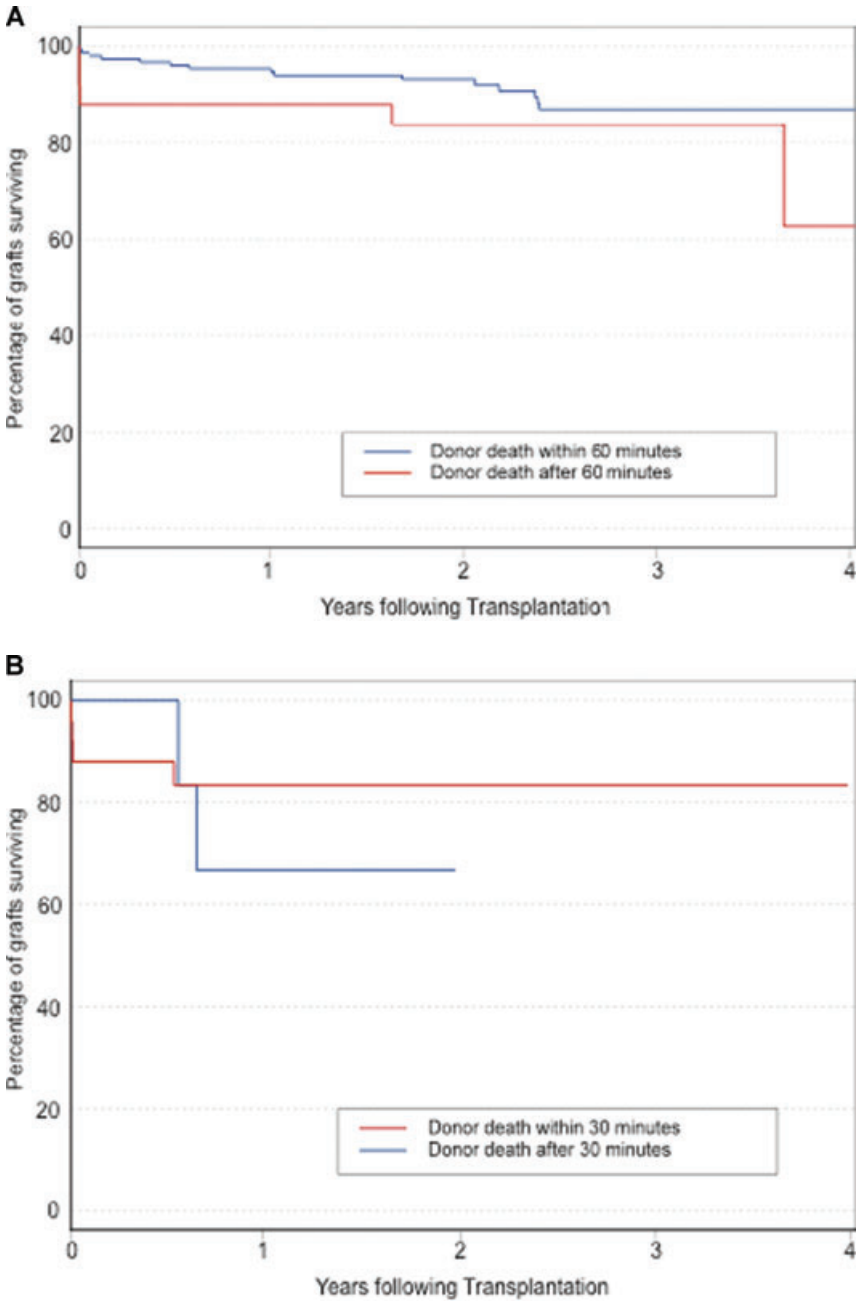


Figure 3: Outcomes of kidneys and livers transplanted from DCD donors. (A) shows the graft survival of kidneys transplanted from donors dying within and beyond 60 min of treatment withdrawal ($p = 0.170$), and (B) shows the graft survival of livers transplanted from donors dying within 30 min and beyond 30 min of treatment withdrawal ($p = 0.493$).

studied only patients where withdrawal of life-supporting treatment included discontinuation from the ventilator or extubation, together with complete cessation of all inotropes. If the practice after deciding to withdraw life-supporting treatment does not include withdrawal of inotropes or involves gradual reduction in ventilatory support, then this will very likely prolong the time to death and reduce the number of patients who are suitable to donate organs for transplantation.

The results from the current study of 191 adult potential DCD donors are broadly in agreement with those from the only other published study of its kind (10). That study, conducted in the USA, included 505 patients, although only 171 of these were under the age of 60 (compared to 176 in our study), the upper age that is often arbitrarily taken as suitable for donation by many transplant centers; in addition many of their patients had other conditions (e.g. cancer) precluding organ donation. Like the present study, the US study showed that the use of inotropes and high FiO_2 were associated with a shorter time to death. It also reported that the use of postwithdrawal sedation (termed 'comfort medicines' by the authors) was associated with a longer time to death and that the mode of ventilation,

Table 1: Cox regression analysis of individual variables which might predict time to death

Variable	Hazard ratio	95% confidence interval	Significance
Sex (reference: Female)			0.875
Male	1.02	0.76–1.37	
Age group (reference ≤30 years)			0.006
31–40	0.56	0.33–0.94	
41–50	0.57	0.37–0.86	
>50	0.48	0.32–0.71	
Cause of death (ref = other)			0.019
Neuro trauma	2.03	1.26–3.27	
Hypoxic injury	1.25	0.74–2.11	
Cerebral bleed	1.48	0.95 to 2.31	
Ventilation* (ref = PS)			<0.001
PC/VC/PRVC	2.09	1.28–3.40	
SIMV(+/−PS)	1.78	1.30–2.44	
Inotrope use (ref = no)			0.001
Yes	1.68	1.25–2.26	
Prior de-saturation (ref = no)			0.669
Yes	1.14	0.69–1.88	
Not performed	1.14	0.84–1.56	
Systolic BP (per mmHg)	0.995	0.991–0.999	0.018
Diastolic BP (per mmHg)	0.995	0.987–1.003	0.209
O_2 saturation (per%)	0.994	0.966–1.021	0.651
Heart rate (per beat/min)	1.003	0.997–1.008	0.347
FiO_2 (per%)	1.014	1.007–1.021	<0.001
pH (per unit increase)	0.121	0.027–0.548	0.009
PaO_2 (per KPa)	1.002	0.977–1.027	0.882
Base excess (per unit)	0.976	0.939–1.015	0.221
PaO_2/FiO_2 ratio (per unit)	0.995	0.986–1.003	0.212

*PS = pressure support; PC/VC/PRVC = pressure control/volume control/pressure regulated volume control; SIMV = synchronized intermittent mandatory ventilation.

use of high levels of positive end expiratory pressure (PEEP), and the mode of treatment withdrawal also affected the time to death. Studies at the University of Wisconsin suggest that age, body mass index and vasopressor use predict early asystole following withdrawal of 'life support'(4), in addition to parameters measured 10 min after treatment withdrawal including respiratory rate and oxygen saturation.

It is important to emphasize that our study aimed to identify the factors predicting an early death following withdrawal of treatment rather than factors that may affect the quality of organs following donation. After treatment withdrawal, the patient might suffer an immediate or very early cardiorespiratory arrest resulting in a short period of hypoxia and hypotension, with the agonal period equating to a period of warm ischemia (illustrated well in Levvey et al. (11)). However it is also possible that the patient may survive many hours after withdrawal of life-supporting treatment with a satisfactory blood pressure and relatively well-perfused organs before a sudden deterioration results in death. In such circumstances, the organs are still likely to be in good condition for transplantation, even though the likelihood is that the recovery team has been stood down. Conversely, many patients who die within 2 h do so in association with a progressive deterioration characterized by a falling blood pressure and consequent poor organ perfusion. Although the organs from such donors might be perfused promptly upon death, they will have sustained sufficient warm ischemia during the agonal phase to render them unusable for transplantation. This scenario highlights another area of DCD donation that needs to be resolved, namely the utility of the term 'warm ischaemic time'. Traditionally, it is taken from the occurrence of asystole until

Table 2: Factors predicting time to death from the Cox multiple variable model

Variable	Hazard ratio	95% confidence interval	Significance
Age group (reference group ≤30 years)			0.001
31–40	0.70	0.38–1.28	
41–50	0.46	0.29–0.76	
>50	0.37	0.23–0.59	
Ventilation (reference: Pressure Support)			0.006
Not Pressure Support	1.67	1.16–2.41	
FiO_2 (per%)	1.012	1.003–1.021	0.008

perfusion with cold preservation solution. We believe that this period is most accurately termed the asystolic warm period (12).

The US conference on DCD donation defined warm ischemic time as including both the asystolic warm period and the time interval from withdrawal of ventilatory support to cardiopulmonary cessation (which they termed the withdrawal phase and which we have termed the agonal phase). This underlies much of the confusion in terminology, since if the donor maintains a good blood pressure and oxygenation the organs will not be ischemic.

A recent retrospective study from Boston underscores the importance of events during this phase (13). They showed that prolonged, severe hypotension following extubation and withdrawal of treatment was associated with more delayed graft function in kidneys and poorer outcomes for livers. Moreover, they suggested that a systolic of less than 50 mmHg for more than 15 min was associated with increased rates of biliary ischemia, graft loss and death following liver transplantation. A similar deleterious effect was seen in kidneys in the same study, where a systolic of less than 70 mmHg was associated with a trend to more delayed graft function ($p = 0.08$).

Given the importance of hypotension in the agonal phase, it would be appropriate to report a further second time period representing the warm ischemia that is sustained, and this might be best termed the agonal warm period. This latter time period could arbitrarily start once the systolic blood pressure falls below a given value, such as 50 mmHg, but there is a necessity to accurately define this threshold value in future studies.

The US conference on DCD donation suggested that potential DCD donors who die more than 60 min after treatment withdrawal are unsuitable kidney donors, and those dying beyond 30 min are unsuitable liver donors. In our study, 17.2% of subjects who became organ donors died beyond 60 min and organs were successfully used from one donor who died 3.3 days following treatment withdrawal. This highlights the importance of describing the events occurring during the agonal period more clearly to enable informed decisions on the safety of transplantation of organs from DCD donor.

One further element seldom reported in connection with DCD organ donation is the need to have an experienced recovery team attending. Minimization of warm ischemia demands rapid cold perfusion of the organs, and then swift but careful dissection to remove the transplantable organs. This is particularly so in combined liver and pancreas recovery where vascular anomalies are less readily detected in the cold and surgical techniques need to be adapted to preserve any aberrant vessels on the assumption that they may be present.

We believe that our study provides guidance for centers with DCD recovery programmes and may assist with planning of resources. We do not propose that the criteria be used to decide which potential donors should be pursued since in an era of organ shortage we should be making maximum effort to retrieve every viable organ (14). Nevertheless, the results may guide resource allocation. Lastly, we believe that there is a great need for a study to explore further the effects of different patterns of deterioration in DCD donors following treatment withdrawal in order that we can properly define the agonal warm period which corresponds to good, and less good, organ transplant outcomes.

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Supporting Information

The following supporting information is available for this article online:

Figure S1: Kaplan–Meier plot showing no difference in time to death for males and females (p = 0.874).

Figure S2: Kaplan–Meier plot showing no difference between patients with normal or low oxygen saturation at the time of withdrawal of cardiorespiratory support (p = 0.662).

Figure S3: Kaplan–Meier plot showing effect of age on time to death (p = 0.002).

Figure S4: Kaplan–Meier plot showing effect of inspired oxygen fraction (FiO_2) on time to death (p = 0.003).

Figure S5: Kaplan–Meier plot showing relationship of arterial pH at withdrawal of cardiorespiratory support and time to death (p = 0.007).

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