Donor cause of death and medium-term survival after heart transplantation: A United Kingdom national study

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Objective: Donor cause of death may be a risk factor for early mortality after heart transplantation, but its effect on medium-term survival is uncertain.

Methods: By means of a national prospective database, we investigated the influence of donor cause of death on survival to 3 years in 1254 adult recipients of cadaveric heart transplantation between July 1995 and June 2002. Donor cause of death was categorized a priori as vascular and tumor (group V, $n = 739$), trauma (group T, $n = 407$), hypoxic (group H, $n = 82$), and infective causes (group I, $n = 26$). Risk factors for early (30-day), late (30-day to 3-year), and overall mortality were identified with Cox regression.

Results: Group V donors were more likely to be older ($P < .001$) and female ($P < .001$). There were 297 deaths in the 3-year period, and the unadjusted 3-year survivals varied significantly (group V 73%, group T 79%, group H 85%, group I 80%, $P = .01$). Cox analysis identified donor age, organ ischemia time, recipient creatinine clearance, recipient diagnosis, peripheral vascular disease, ventilation, diabetes, and donor-recipient size mismatch as risk factors for early, late, or overall mortality ($P < .10$). After adjustment for these factors, donor cause of death was no longer a significant predictor of recipient death (early death $P = .36$, late death $P = .79$, overall mortality $P = .37$).

Conclusion: We confirmed that there is an apparent association between cause of donor death and posttransplantation survival, but this was not maintained after adjustment for confounding variables. Donor cause of death therefore should not influence donor organ acceptance or donor-recipient matching and does not identify marginal donors.

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The quality of the donor heart has an effect on the outcome of heart transplantation, as shown by the inferior results when hearts from older or marginal donors have been used.¹ Intracranial vascular events as the donor cause of death (DCD) may be a risk factor for early mortality after heart transplantation, but there is conflicting evidence regarding the cause of donor brainstem death on longer-term outcome.²⁻⁵ The size and statistical power of some of these reports may have limited their ability to identify important effects.⁴

Experimental studies have shown that very abrupt brain death adversely affects the physiology of the heart, primarily as a result of the catecholamine surge.^{6,7} The deleterious effect of brain death on heart function appears to increase with the acuity of intracranial pressure rise.^{8,9} In addition, brainstem death results in an inflammatory response, with upregulation of proinflammatory cytokines and adhesion molecules and rapid leukocyte infiltration. These may exacerbate myocyte injury and are associated with accelerated acute rejection after heart transplantation in animals.¹⁰ Although there is evidence that DCD is a risk factor for early mortality after heart transplantation, it is unclear whether this effect is independent of other factors.

Figure 1. Study population and DCD groups.

TABLE 1. Pretransplantation donor characteristics grouped by DCD

	Group V (n = 739)		Group T (n = 407)		Group H (n = 82)		Group I (n = 26)		P value
Age (y, median and IQR)	41	32-48	24	19-34	26	20-37	22	18-33	.001
Male (No.)	412	56%	327	80%	42	51%	20	77%	.001
Cytomegalovirus positive (No.)*	326	44%	197	49%	26	32%	9	35%	.02
Height (cm, median and IQR)*	173	165-180	176	170-182	172	165-180	177	170-180	.001
Weight (kg, median and IQR)*	70	65-80	72	65-80	70	60-80	75	59-87	.3
Body mass index (kg/m ² , median and IQR)*	24	22-27	23	22-25	23	21-26	24	20-26	.003

Group V, Vascular and tumor DCD; Group T, traumatic DCD; Group H, hypoxic DCD; Group I, infective DCD; IQR, interquartile range. *Less than 1% missing data.

Moreover, the nature of DCD may vary among regions and countries,¹¹ with absence of gunshot wounds to the head in the United Kingdom.¹² To identify variations in DCD in the United Kingdom and to investigate the influence of DCD on medium term survival to 3 years, we analyzed data from the UK Cardiothoracic Transplant Audit database.

Methods

The United Kingdom Cardiothoracic Transplant Audit is a national prospective cohort study that has been collecting data since April 1995 on all intrathoracic transplantation procedures in the United Kingdom. Data are collected when patients are registered on the national waiting list for heart transplantation, at the time of transplantation, and at selected (90 days and yearly thereafter) follow-up periods. Regular computer-based and on-site case-record validations are undertaken to ensure accuracy and consistency of data and the follow-up is 100% complete.

In this study, adult (age ≥16 years), first-time, isolated heart recipients undergoing cadaveric donor organ transplantation between July 1995 and June 2002 were analyzed. The age for defining pediatric recipients is 16 years in the United Kingdom, as defined in the “Donor Organ Sharing Scheme—Operating Principles for Cardiothoracic Transplant Units in the UK and Republic of Ireland.”¹³ Survival to 3 years was taken as the primary end point of the study. DCD was categorized a priori into four categories: cerebrovascular accidents and brain tumors, cerebral trauma, hypoxic brain damage, and infective causes.

Donor and recipient characteristics were compared with the χ^2 test (categorical data) or the Kruskal-Wallis test (continuous variables). The Kaplan-Meier method was used to derive the survival estimates. Survival across the DCD groups was compared with the Wilcoxon-Breslow test. Cox proportional hazards regression analysis¹⁴ was used to identify risk factors for three periods: early

(30-day), late (30-day to 3-year), and overall (3-year) survivals. These three epochs were chosen to represent clinically meaningful periods of posttransplantation time and to contain approximately equal numbers of deaths in each period. The Cox model for each time period was developed in stages. Potentially important variables, identified from a clinical review of the database, were first fitted with a stepwise procedure with a cutoff for variable inclusion of $P = .10$. Variables identified in any of the three models were included in all the models to allow comparison of results in the different epochs. All analyses were stratified by center size (two strata) to allow for differing baseline hazard between high- and low-volume centers. DCD was then added to the model, thereby allowing us to examine the effect of DCD on survival after controlling for the variables identified from the stepwise procedure. The proportional hazards assumption was checked for all models fitted. Results are presented as hazard ratios with 95% confidence intervals (CIs). Statistical analyses were carried out with Stata statistical software (release 8.2; Stata Corporation, College Station, Tex).

Results

A total of 1254 adult recipients undergoing first-time cardiac transplantation, excluding multiorgan transplantation, from cadaveric donors between July 1995 and June 2002 were studied. There were 739 (59%) heart transplants from donors who died of vascular and tumor-related causes, 407 (32%) from donors who died after trauma, 82 (7%) from donors who died of hypoxic brain injury (including drug overdose), and 26 (2%) from donors with infective causes of death (Figure 1). Detailed causes of death for donors assigned to each of the four groups are given in Appendix Table 1. Brain tumor as DCD constituted 5% of the V group.

TABLE 2. Pretransplantation recipient characteristics grouped by DCD

	Group V (n = 739)		Group T (n = 407)		Group H (n = 82)		Group I (n = 26)		P value
Recipient age at transplantation (median and IQR)	52	45-57	51	42-56	50	42-55	51	48-56	.2
Male recipient (No.)	614	83%	346	85%	60	73%	20	77%	.06
Recipient height (cm, median and IQR)*	173	167-178	174	168-179	172	165-176	175	165-178	.08
Recipient weight (kg, median and IQR)	75	66-85	76	67-86	76	65-83	79	68-89	.5
Recipient body mass index (kg/m ² , median and IQR)	25	23-28	26	23-28	26	23-28	26	23-30	.5
Previous heart operations (No.)*	254	34%	105	26%	26	32%	7	27%	.02
Serum creatinine (μmol/L, median and IQR)*	116	98-136	118	98-141	112	100-137	129	100-169	.4
Creatinine clearance (mL/min, median and IQR)*	71	56-87	71	57-90	68	56-90	62	53-87	.7
Inpatient at transplantation	162	22%	78	19%	18	22%	5	19%	.7
Inotropes at transplantation*	103	14%	52	13%	11	13%	3	12%	.9
Intra-aortic balloon pump at transplantation*	28	4%	11	3%	4	5%	1	4%	.5

Group V, Vascular and tumor DCD; Group T, traumatic DCD; Group H, hypoxic DCD; Group I, infective DCD; IQR, interquartile range. *Less than 1% missing data.

TABLE 3. Recipient causes of death in the DCD cohorts

Cause of death	Group V	Group T	Group H	Group I	Total
Cardiac failure (including rejection and cardiac allograft vasculopathy)	48 (25%)	16 (19%)	1 (8%)	1 (20%)	66 (22%)
Early graft failure*	57 (29%)	23 (28%)	5 (42%)	1 (20%)	86 (29%)
Hemorrhage including gastrointestinal hemorrhage	11 (6%)	3 (3%)	0 (0%)	0 (0%)	14 (5%)
Infection	27 (14%)	10 (13%)	2 (17%)	1 (20%)	40 (13%)
Embolism or infarction	14 (7%)	3 (3%)	0 (0%)	0%	17 (6%)
Multiorgan failure	13 (6%)	11 (13%)	2 (17%)	0%	26 (9%)
Malignancy	4 (2%)	3 (3%)	1 (8%)	0%	8 (3%)
Other causes of death	9 (5%)	9 (11%)	1 (8%)	1 (20%)	20 (7%)
Cause of death unknown	13 (6%)	6 (7%)	0 (0%)	1 (20%)	20 (7%)
Total	196 (100%)	84 (100%)	12 (100%)	5 (100%)	297 (100%)

Group V, Vascular and tumor DCD; Group T, traumatic DCD; Group H, hypoxic DCD; Group I, infective DCD. *Deaths due to donor organ failure in that admission for transplantation.

Donor and pretransplantation recipient characteristics were compared across the four groups, and some differences were found (Tables 1 and 2). Donors dying of vascular and tumor causes were significantly older than donors dying of other causes ($P < .001$), and the trauma and infective groups had a higher proportion of male donors than the other groups ($P < .001$). Also, donors in these groups were taller ($P < .001$) and had a lower body mass index ($P = .003$) than those in the other two groups. Significantly fewer donors dying of hypoxic brain damage or infective causes had positive antibodies for cytomegalovirus than in the other groups.

The proportion of male recipients was higher in the vascular and trauma groups, but not significantly so ($P = .06$). Previous

heart surgery, defined as any procedure where the use of cardiopulmonary bypass was employed, was more common among recipients in the vascular and hypoxic brain injury groups ($P = .02$). All other factors were distributed similarly across the four groups.

At analysis, 297 (24%) patients had died, and the overall 3-year survival for the whole cohort was 75% (95% CI 73%-78%). The causes of death for recipients did not differ among the DCD cohorts (χ^2 test, $P = .7$; Table 3). The median follow-up for survivors was 36 months. Unadjusted Kaplan-Meier survival estimates by DCD are shown in Figure 2. Three-year survival differed significantly across the groups ($P = .01$). Recipients of hearts from donors who

Numbers at risk	Transplant	30 days	Year 1	Year 2
Vascular & tumour	739	636	544	468
Trauma	407	369	334	301
Hypoxic brain injury	82	76	70	60
Infective	26	24	21	14

Figure 2. Unadjusted Kaplan-Meier survival estimates by DCD groups ($P = .01$).

had died of vascular and tumor causes had the lowest 3-year survival (73%, 95% CI 69%-76%), and survival was highest in the hypoxic brain injury group (85%, 95% CI 75%-91%). Three-year survival of recipients with hearts from the traumatic group was 79% (95% CI 74%-83%).

Stepwise Cox regression analysis identified donor age (grouped <25 years, 26-40 years, 41-55 years, >55 years), organ ischemia time (grouped <120 minutes, 121-180 minutes, 181-240 minutes, >240 minutes), recipient creatinine clearance at transplant (<50 mL/min), recipient diagnosis (grouped ischemic cardiomyopathy, dilated cardiomyopathy, congenital cardiac disease, other cardiac diseases), history of peripheral vascular disease in the recipient, recipient ventilation before or at the time of transplantation, diabetes (in the donor and in the recipient), drug abuse in the donor, and donor-recipient size mismatch (ratio of donor to recipient body surface area <0.80) as risk factors for early, late, or overall mortality ($P < .10$). Estimated hazard ratios for recipient factors and DCD are given in Table 4 and those for donor factors and DCD are given in Table 5. Preoperative ventilation was included only in the early (30-day) survival model, because all recipients with preoperative ventilation died within 30 days of transplantation. After adjustment for the factors iden-

tified from the stepwise analyses, DCD was no longer a significant predictor of recipient death (early death $P = .36$, late death $P = .79$, overall mortality $P = .37$).

The proportional hazards assumption was checked for the three models. The overall test for each model suggested that the assumption was reasonable (test for nonproportionality $P = .22$, $P = .29$, and $P = .69$ for overall, 30-day, and 30-day to 3-year models, respectively).

Discussion

Unlike previous studies, we have found that the apparent association between DCD and recipient survival does not persist after adjustment for other covariates. In keeping with previous studies, the donor organ characteristics that determine early outcome are donor age, ischemia time, and size mismatch.^{1,15} After the initial 30 posttransplantation days, the only donor factor determining 3-year outcome is donor age. Some earlier studies have reported an association between DCD and posttransplantation survival.^{3,5,10} Tsai and colleagues³ compared outcomes in heart transplant recipients of donors with traumatic and atraumatic intracranial bleeding. They found significantly worse early posttransplantation survival in the atraumatic group but no difference

TABLE 4. Recipient risk factors for early (<30-day), late (30-day to 3-year), and overall survivals

Risk factor	Early			Late			Overall		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Creatinine clearance	1.88	1.29-2.73	.001	1.04	0.67-1.62	.9	1.43	1.08-1.90	.01
Diabetes mellitus	2.21	1.38-3.53	.001	0.78	0.38-1.60	.5	1.48	1.01-2.19	.05
Ventilation*	2.43	0.98-6.03	.06	—	—	—	—	—	—
Peripheral vascular disease	3.30	1.50-7.27	.003	0.53	0.07-3.81	.5	1.93	0.94-3.95	.07
Diagnosis group									
Ischemic cardiomyopathy	1	—	.01	1	—	.1	1	—	.03
Dilated cardiomyopathy	0.83	0.57-1.20		0.76	0.53-1.10		0.79	0.61-1.02	
Congenital heart disease	2.73	1.36-5.46		0.51	0.12-2.12		1.58	0.86-2.89	
Other heart disease	1.08	0.65-1.79		1.34	0.84-2.15		1.20	0.85-1.69	

*Inestimable hazard ratios.

in long-term mortality. Busson and associates,⁵ by both univariate and multivariate analysis in a multicenter study, found better medium-term (2-year) survival with hearts from donors who died of intracranial injury than with those who died of cerebral hemorrhage.

In experimental studies, myocardial injury after brainstem death varies significantly with the type and duration of brain injury.^{8,16} Our a priori classification of DCD (vascular and tumor, trauma, hypoxic brain damage, and infection) assumed different pathophysiologic mechanisms of brainstem death in the different groups. As in previously published reports, we assumed that donors in the two larger categories (vascular and tumor and trauma) might experience a different acuity of brainstem death. The hypoxic brain injury and infection (predominantly meningitis) groups were considered separately because their pathophysiologic characteristics could not be presumed to be similar to those of the major groups. In the United Kingdom, most posttrauma donors are killed in motor vehicle crashes (there were no gunshot wounds to the head in this series). These donors potentially have a more rapid development of intracranial pressure than those in the vascular and tumor group

and also could have been expected to include a significant fraction of donors with multiple injuries. We included donors who died of tumor in the vascular group on the assumption that they would have a single organ process and a similar timescale of brainstem death development. A post hoc analysis revealed near identical results when donors with vascular cause of death were considered separately.

In this study, donors dying of vascular accidents and brain tumors were significantly older than other donors. Posttrauma donors were younger, more likely to be male, and taller than donors from other groups, with a lower body mass index. These factors (age, sex, and size) are potentially advantageous for the outcome in the trauma group and, we believe, led to the improved unadjusted survival. This apparent association between DCD and survival after heart transplantation was not confirmed after adjustment for donor- and recipient-related confounding factors. Importantly, this cohort did not include any patients with extremely acute trauma from gunshot wounds to the head. The latter group could have a different pathophysiology and acuity of brainstem death, which could influence survival. We also found statistically significant differences on univariate analysis in donor cytomegalovirus status

TABLE 5. Donor risk factors for early (<30-day), late (30-day to 3-year), and overall survivals

Risk factor	Early			Late			Overall		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
DCD									
Vascular and tumor	1	—	.4	1	—	.8	1	—	.4
Trauma	0.76	0.50-1.16		1.04	0.70-1.55		0.88	0.66-1.18	
Hypoxic brain injury	0.57	0.25-1.33		0.67	0.29-1.56		0.61	0.34-1.12	
Infective	0.54	0.13-2.22		1.07	0.33-3.45		0.73	0.30-1.81	
Donor age group*	1.24	0.99-1.53	.05	1.30	1.06-1.62	.01	1.26	1.09-1.47	.002
Donor drug abuse†	0.74	0.23-2.37	.2	1.61	0.69-3.74	.2	1.12	0.57-2.22	.09
Donor diabetes†	1.11	0.27-4.58	.1	0.76	0.18-3.13	.5	0.92	0.34-2.51	.07
Size mismatch	2.95	1.19-7.31	.02	0.50	0.07-3.58	.5	1.63	0.72-3.69	.2
Organ ischemia time	1.36	1.13-1.64	.001	1.16	0.97-1.40	.1	1.26	1.10-1.43	.001

*Increase in each age group. †Adjusted for missing values.

and in the history of previous open heart operations in recipients. These findings are difficult to explain and may represent type I statistical errors.

This study is based on a multicenter national cohort of patients with 100% data accrual and follow-up. The end point of survival is robust and validated. However, we were not able to validate a timescale for donor brainstem death, and we recognize that this may be important. Although the study represents a retrospective analysis, the data were accrued prospectively. We were not able to assess the severity of the rejection episodes or development of graft vasculopathy, because the database was set up to collect a limited number of variables for audit purposes. The differences in transplantation volume among the centers was allowed for in the proportional hazards model.

In conclusion, although there is an apparent association between DCD and posttransplantation survival, it is not maintained after adjustment for confounding variables. DCD was not an independent risk factor for mortality as late as 3 years after heart transplantation in this national cohort.

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Appendix

TABLE 1. Individual DCDs by DCD group

Cause of death	No.	%
Cause of death in vascular and tumor group (n = 739)		
Intracranial hemorrhage	628	85%
Intracranial thrombosis	22	3%
Brain tumor	37	5%
Intracranial, type unclassified (cerebrovascular accident)	41	6%
Aneurysm	10	1%
Liver failure (not self-poisoning)	1	—
Cause of death in trauma group (n = 407)		
Trauma, road traffic accident, car	98	24%
Trauma, road traffic accident, motorbike	48	12%
Trauma, road traffic accident, bicycle	28	7%
Trauma, road traffic accident, pedestrian	73	18%
Trauma, road traffic accident, unknown type	41	10%
Other trauma, accident	96	24%
Other trauma, unknown cause	23	5%
Cause of death in hypoxic brain injury group (n = 82)		
Hypoxic brain damage, all causes	33	40%
Other trauma, suicide	25	30%
Cardiac arrest	4	5%

Cause of death	No.	%
Asthma	3	4%
Respiratory failure	3	4%
Carbon monoxide poisoning	5	6%
Respiratory type unclassified, including smoke inhalation	1	1%
Acetaminophen (INN: paracetamol) overdose	1	1%

Cause of death	No.	%
Other drug overdose	7	9%
Cause of death in infective group (n=26)		
Meningitis	19	73%
Septicemia	1	4%
Infections, type unclassified	6	23%

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