

# Is donation after cardiac death reducing the brain-dead donor pool in Australia?

Brett G Sampson, Gerry P O'Callaghan and Graeme R Russ

Donation after brain death (DBD) is preferred to donation after cardiac death (DCD) because the number of viable organs per donor is higher, the logistics of the donation process are simpler and transplant outcomes are optimised.<sup>1,2</sup> DCD provides an additional opportunity for donation in patients with non-survivable brain injury who do not progress to brain death.<sup>1-4</sup> In recent years, controlled DCD programs have been introduced throughout Australia in an attempt to meet the shortfall in available organs for transplantation, culminating in the release of the National Protocol for DCD in 2010.<sup>4,5</sup>

DCD numbers are now increasing more rapidly than DBD numbers.<sup>6</sup> This is despite national efforts to increase organ donation via both pathways.<sup>7</sup> Importantly, there is a wide disparity between jurisdictions, with Victoria, New South Wales and Queensland having the fastest increase in DCD numbers.<sup>6</sup> Although this increase in DCD is likely to represent a previously unrealised donor pool, there is concern that it might represent the conversion of potential brain-dead donors into DCD donors, especially in the jurisdictions with the highest DCD numbers. The introduction of controlled DCD programs internationally has seen DBD numbers fall in the United Kingdom, United States, Belgium, Netherlands and South Korea.<sup>8-14</sup> It has been widely suggested that advances in the neurosurgical and intensive care management of brain injury is preventing progression to brain death in some patients, resulting in fewer brain-dead donors and possibly more potential DCD donors.<sup>14,15</sup> However, it is not known how many brain-injured DCD donors would have otherwise progressed to brain death.

Brain death occurs in severely brain-injured patients when intracranial pressure rises above systemic blood pressure, stopping blood flow to the whole brain.<sup>1</sup> The final common pathway is a cycle of cerebral oedema and ischaemia, resulting in incremental increases in intracranial pressure.<sup>1</sup> The time to then progress to brain death is highly variable, depending on the cause of brain injury, treatment received and individual patient factors. Brain death can evolve rapidly, such as after a catastrophic intracranial haemorrhage, or slowly, as in hypoxic brain injury. Unfortunately, it is not possible to predict with any certainty when, and in whom, brain death will occur. Therefore, there is a risk of proceeding to DCD without allowing sufficient time for progression to brain death, resulting in the unintentional loss of potential brain-dead donors.

## ABSTRACT

**Background:** Donation after cardiac death (DCD) has increased faster than donation after brain death (DBD) in Australia. However, DBD is the preferred pathway because it provides more organs per donor, the donation process is simpler and transplant outcomes are optimised.

**Objective:** To determine if the increase in DCD has reduced the brain-dead donor pool in Australia.

**Design, setting and participants:** Retrospective analysis of records of organ donors (intended and actual) with brain injury as the cause of death from 2001 to 2011 in Australian intensive care units.

**Main outcome measures:** Change in median ventilation period, over time, before brain-death determination in DBD donors (as DCD increased); a decreased median ventilation period in DBD donors being consistent with the conversion of DBD to DCD.

**Results:** As DCD ( $n = 311$ ) increased, the median ventilation period in DBD donors ( $n = 2218$ ) did not fall overall ( $P = 0.83$ ), in all jurisdictions ( $P > 0.25$ ) and for all causes of death ( $P > 0.3$ ). The proportion of patients ventilated for less than 2 days was unchanged over time in both DBD ( $P = 1$ ) and DCD ( $P = 0.99$ ). The overall ventilation period in DCD donors (3.8 days; interquartile range [IQR], 2.1–6.3 days), exceeded the ventilation period in DBD donors (1.3 days; IQR, 1.0–2.4 days;  $P < 0.0001$ ). DCD ventilation period was significantly longer in all jurisdictions, for all causes of death and annually ( $P < 0.05$ ).

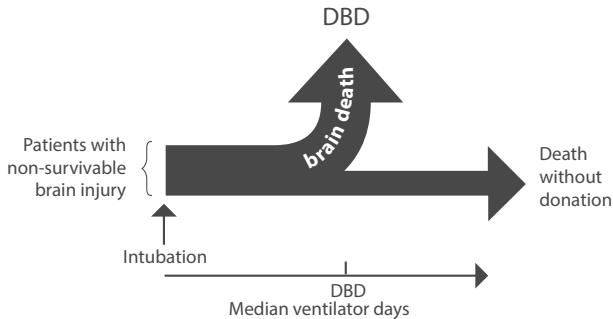
**Conclusions:** In Australia, brain-injured donors appear to be ventilated long enough to allow progression to brain death before proceeding to DCD. Therefore, DCD is unlikely to have reduced the brain-dead donor pool.

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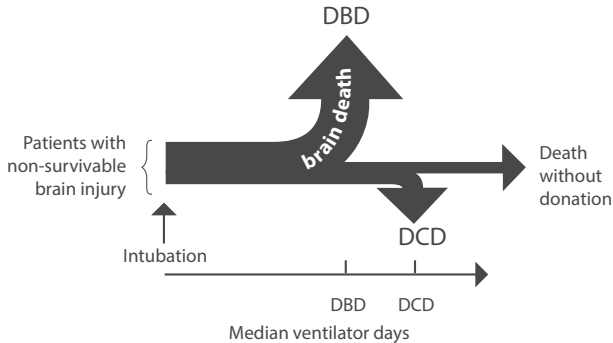
We hypothesised that DCD is reducing the brain-dead donor pool in Australia. To test this hypothesis, we analysed the effect of the increasing numbers of DCD donors on the ventilation period in brain-dead donors (Figure 1). We expected to find a decreased median ventilation period in brain-dead donors over time, which would be consistent with the conversion of some potential brain-dead donors into DCD donors.

**Figure 1. Schematic representation of the potential effect of DCD on the brain-dead donor pool, using ventilation period as an outcome measure**

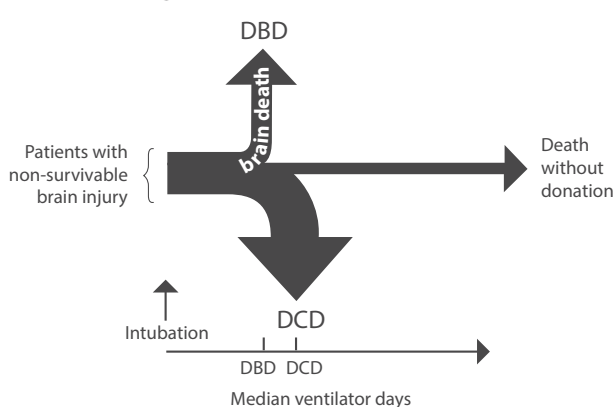
A) DBD donation without DCD



B) DCD without reducing DBD donors



C) DCD reducing DBD donors



DBD = donation after brain death. DCD = donation after cardiac death. A. When donation only occurs after brain death, there is an unrealised potential DCD donor pool. B. When DCD only proceeds after sufficient time is allowed for brain death to occur, brain-dead donors are not lost and the median ventilation period in DBD donors does not change. C. When DCD proceeds too early, there is a loss of potential brain-dead donors and the median ventilation period in DBD donors falls (as those donors requiring longer to become brain dead are preferentially lost to DCD).

**Methods**

We performed a retrospective analysis of prospectively collected data from the Australian and New Zealand Organ Donor (ANZOD) registry from 2001 to 2011.<sup>6</sup> Ethics approval was granted by the Southern Adelaide Clinical Human Research Ethics Committee (application 421.11).

**Patients**

We included adult and paediatric solid-organ donors (intended and actual), in Australia, with brain injury as the cause of death. Intended donors were defined as those for whom consent for donation had been obtained but who did not then proceed to organ procurement. DCD donors who did not have a brain injury as the cause of death were excluded. Cause of death was categorised as cerebrovascular accident (CVA), traumatic brain injury (trauma), hypoxic brain injury (hypoxia) and other brain injury (eg, brain tumours, central nervous system infections).

**Determination of brain death**

Determination of brain death was in accordance with the Australian and New Zealand Intensive Care Society (ANZICS) statement on death and organ donation.<sup>1</sup> Brain death was determined by clinical testing of brainstem function or demonstration of the absence of intracranial blood flow (by radionuclide imaging or intra-arterial cerebral angiography).

**Donation after cardiac death**

All DCDs were controlled, with planned withdrawal of life-sustaining treatment (WLST) in physiologically stable patients with non-survivable brain injury (Maastricht category III).<sup>3,4</sup>

**Ventilation period**

The ventilation period in DBD was measured from the time of endotracheal intubation to the time of determination of brain death in both actual and intended brain-dead donors. For the purposes of our study, the time when the DBD pathway was taken was represented by the time of determination of brain death (ie, no brain-dead donor proceeded to DCD). The ventilation period from brain-death determination to organ procurement was intentionally excluded for outcome analysis, as it is dependent on factors not related to the clinical decision to follow the DBD pathway. However, the ventilation period from intubation to organ procurement in brain-dead donors (actual donors only) was also calculated using aortic cross-clamp time as the end point.

The ventilation period in DCD was measured from endotracheal intubation to the time of WLST. ANZOD has only been recording times of WLST since January 2008, so

**Table 1. Characteristics of intended and actual donors**

Patient characteristic	DBD (n = 2218)	DCD* (n = 311)	P
Median age (years) (interquartile range)	46.7 (30–58.7)	48.3 (33.9–59)	0.08
Paediatric patients <sup>†</sup>	199 (9%)	12 (3.9%)	< 0.0001
Male	1268 (57.2%)	209 (67.2%)	0.0007
Intended:actual donors	85:2133	71:240	0.0001
Cause of death			
CVA	1176 (53%)	104 (33.4%)	< 0.0001
Hypoxia	394 (17.8%)	110 (35.4%)	< 0.0001
Trauma	554 (25%)	89 (28.6%)	0.12
Other brain injury	94 (4.2%)	8 (2.6%)	0.22

DBD = donation after brain death. DCD = donation after cardiac death. CVA = cerebrovascular accident. \* DCD with brain injury as a cause of death. † < 18 years.

we estimated WLST for actual donors before 2008 by subtracting 90 minutes (the longest acceptable time for organ procurement) from the aortic cross-clamp time to give the shortest possible ventilation duration. We excluded intended DCD donors before 2008 because WLST could not be estimated.

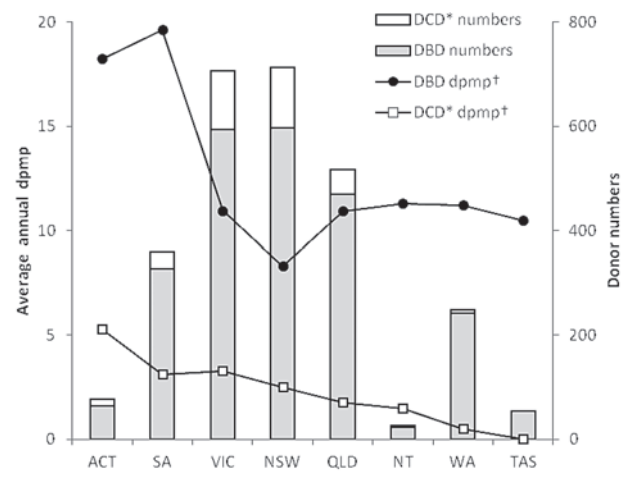
If the date of ventilation initiation was not recorded, the donor was excluded. If the ventilation date was known but the time was unrecorded, the time was taken as either the admission time (if it occurred on the same day) or 12am (if ventilation date occurred after the admission date).

### Ventilation period over time

The primary outcome measure was the change, over time, in ventilation period before determination of brain death in DBD (as DCD numbers increased). We also analysed the change in DBD ventilation period before organ procurement; the change in DCD ventilation period over time; and the proportion of donors ventilated for less than 2 days before brain-death determination in DBD, and before WLST in DCD.

### Statistical analysis

Categorical data were analysed with the Fisher exact test for comparisons within and between DCD and DBD groups. Continuous data were tested for normality with the Shapiro–Wilk normality test. Non-parametric tests were used for non-normally distributed data. The Mann–Whitney U test was used to compare ventilation periods for DCD and DBD donors, by jurisdiction (Australian states and territories), cause of death and year. The Kruskal–Wallis test was used to compare median ventilation periods over time. The  $\chi^2$  test was used to compare, over time, the proportion of

**Figure 2. Donor numbers and average donors per million population per year, by jurisdiction, 2001–2011**

DCD = donation after cardiac death. DBD = donation after brain death. dpmpt = donors per million population. ACT = Australian Capital Territory. SA = South Australia. VIC = Victoria. NSW = New South Wales. QLD = Queensland. NT = Northern Territory. WA = Western Australia. TAS = Tasmania. \* DCD with brain injury as the cause of death. † Annual dpmpt<sup>16</sup> for DBD was averaged over 2001–2011; for DCD was averaged over 2005–2011.

donors ventilated for less than 2 days. A *P* value of < 0.05 was considered significant. SPSS version 19 (SPSS Inc) was used for statistical analysis.

## Results

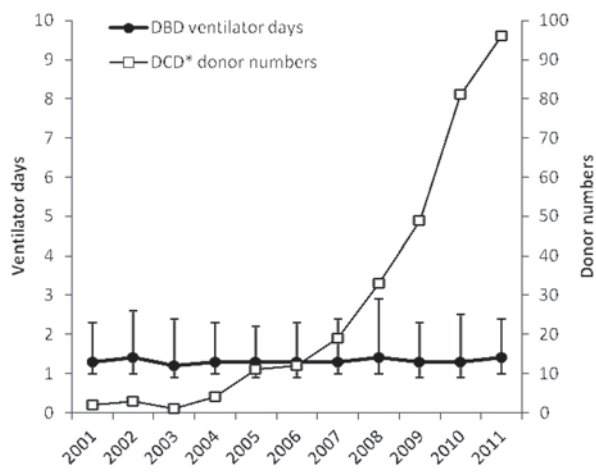
### Participants

Of the eligible donors (2374 DBD and 330 DCD), we included 2218 DBD donors and 311 DCD donors. Exclusions from both groups were all due to an inability to calculate the ventilation period. Intended donors accounted for nine out of 156 excluded DBD donors and 16 out of 19 excluded DCD donors. No donor determined to be brain dead donated via the DCD pathway. All DCDs were from controlled, Maastricht category III donors.<sup>3,4</sup> Donor characteristics are shown in Table 1, and Figure 2 shows donor numbers and the average annual donors per million population for all jurisdictions.

### Ventilation period

The median ventilation period of all DCD donors before WLST was 3.8 days (interquartile range [IQR], 2.1–6.3 days), which was significantly longer than the median ventilation period before brain-death determination in all DBD donors (1.3 days; IQR, 1.0–2.4 days; *P* < 0.0001). DCD donors were still ventilated for a significantly longer period than DBD

**Figure 3. Ventilation period before brain-death determination in brain-dead donors and DCD donor numbers, per year in Australia, 2001–2011**



DCD = donation after cardiac death (DCD donor numbers are shown as absolute numbers per year). DBD = donation after brain death (DBD ventilator days are shown as medians with interquartile ranges); Kruskal–Wallis test was used to compare the annual median DBD ventilation period ( $P=0.83$ ). \*DCD with brain injury as the cause of death.

donors ( $n=2133$ ) when organ procurement was used as the ventilation end point (median ventilation period, 2.3 days; IQR, 1.88–3.35 days;  $P<0.001$ ). The proportion of all DBD donors ventilated for less than 2 days before brain-death determination (68%) was significantly higher than the proportion of all DCD donors ventilated for less than 2 days before WLST (20.9%;  $P<0.001$ ).

There was a significantly longer period of ventilation in DCD donors in all Australian jurisdictions (NSW, Victoria, Queensland and South Australia,  $P<0.0001$ ; Australian Capital Territory  $P=0.002$ ; and Western Australia  $P=0.003$ ), for all causes of death (CVA, hypoxia and trauma,  $P<0.0001$ ; other,  $P=0.03$ ) and annually from 2005 to 2011 (all  $P$  values  $<0.002$ ).

There was no significant difference in the overall median ventilation period of DBD donors between jurisdictions ( $P=0.29$ ). DBD donors dying from hypoxia had a significantly longer ventilation period before brain-death determination (2 days; IQR, 1.2–3.1 days), when compared with DBD donors dying from CVA (1.2 days; IQR, 0.9–2.0 days;  $P<0.0001$ ), trauma (1.3 days; IQR, 0.9–2.7 days;  $P<0.0001$ ), and other brain injury (1.5 days; IQR, 0.9–2.9 days;  $P<0.02$ ). In DCD donors, there was no significant difference in ventilation periods when causes of death were compared ( $P=0.07$ ).

### Ventilation period over time

There was no significant change in the median ventilation period before brain-death determination in DBD donors

over the study period ( $P=0.83$ ) (Figure 3). This was consistent in all jurisdictions and for all causes of death (Figures 4 and 5). There was no significant change over time in the ventilation period before organ procurement in DBD donors ( $P=0.23$ ) or before WLST in DCD donors ( $P=0.12$ ). There was no significant change over time in the proportion of patients ventilated for less than 2 days in DBD donors ( $P=1.0$ ) nor in DCD donors ( $P=0.99$ ).

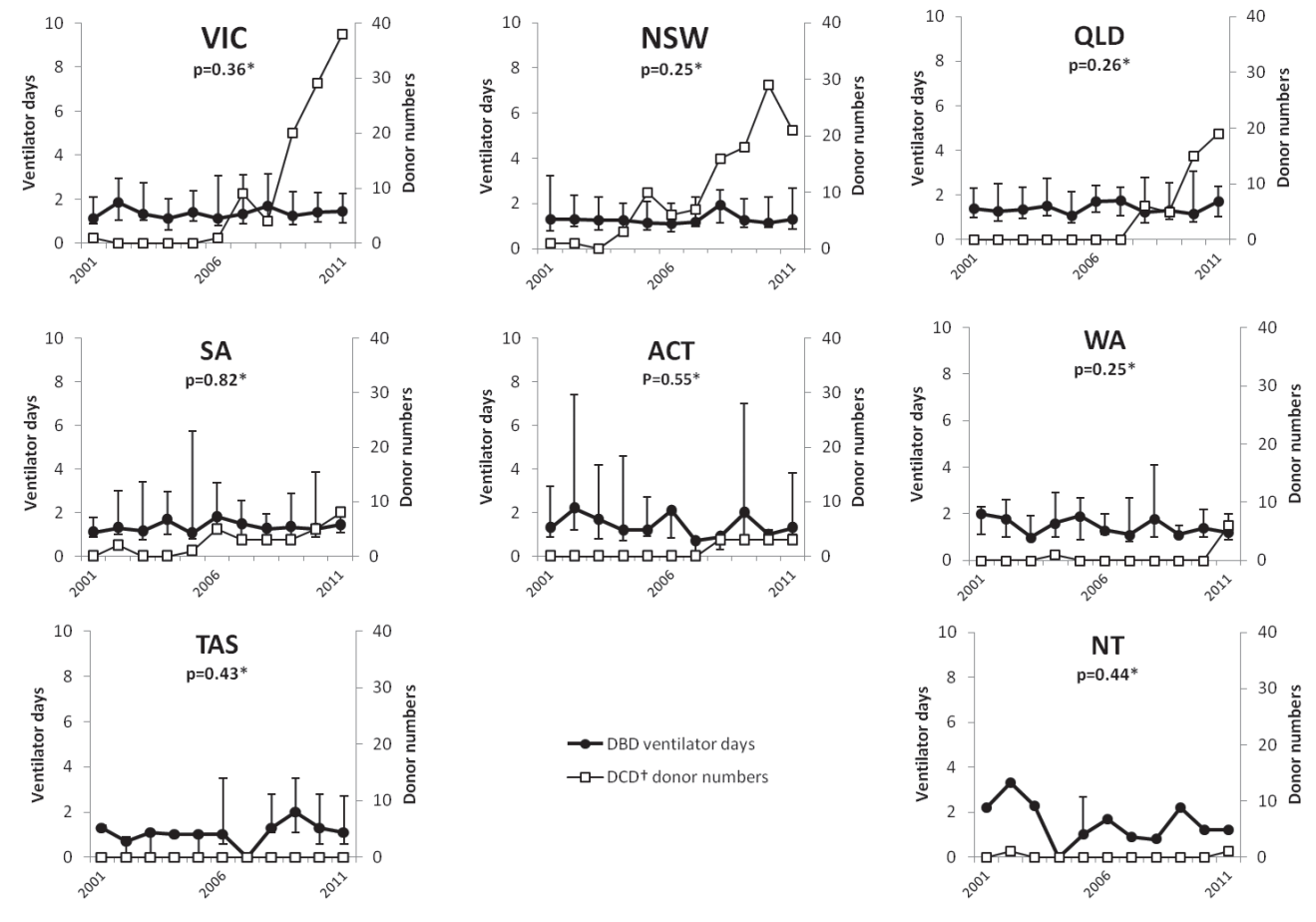
### Discussion

We found that the ventilation period in brain-dead donors before brain-death determination (and before organ procurement) did not fall with the introduction of DCD programs throughout Australia. Also, the proportion of donors ventilated for less than 2 days did not change as DCD donor numbers increased. The ventilation period in DCD donors exceeded the ventilation period in DBD donors for all causes of death, and annually from 2005. These findings suggest that Australian intensive care doctors have allowed sufficient time for brain death to occur before proceeding to DCD. It is therefore likely that DCD donors in Australia represent a previously unrealised donor pool, and not the loss of potential brain-dead donors.

The overall median DBD ventilation period did not differ significantly between jurisdictions. Also, the DBD ventilation period did not change over time in any Australian state or territory, despite the wide disparity between jurisdictions in the rate of increase and total number of DCD donors. These important findings suggests a nationally consistent approach to the timing of brain-death determination in DBD donors, which appears to be unaffected by the varying DCD activity between jurisdictions. The rapid increase in DCD donors seen in Victoria, NSW and Queensland is likely to be the result of successful implementation of DCD programs within individual intensive care units,<sup>5</sup> resulting in few missed potential DCD donors and high consent rates. Possible explanations for low DCD numbers include unsuccessful (or nonexistent) DCD programs, frequently missed potential DCD donors, high rates of family refusal, and not offering DCD unless donation is raised by the family. Future research is required to fully elucidate the vast discrepancy in DCD numbers between Australian jurisdictions.

Investigators in Europe,<sup>11</sup> the UK<sup>14</sup> and the US<sup>15</sup> concluded that the fall in DBD numbers in their countries has resulted from a fall in the incidence in brain death, rather than brain-dead donors being lost to DCD. It has been widely suggested that advances in neurosurgical and intensive care management of severe brain injury is preventing progression to brain death in some patients,<sup>11,14,15</sup> resulting in a fall in brain-dead donors and an increase in potential DCD donors. However, in many European countries without

**Figure 4. Ventilation period before brain-death determination in brain-dead donors, and DCD donor numbers per year, by jurisdiction, 2001–2011**



DCD = donation after cardiac death (DCD donor numbers are shown as absolute numbers per year). DBD = donation after brain death (DBD ventilator days are shown as medians with interquartile ranges). VIC = Victoria. NSW = New South Wales. QLD = Queensland. SA = South Australia. ACT = Australian Capital Territory. WA = Western Australia. TAS = Tasmania. NT = Northern Territory. \* Kruskal–Wallis test was used to compare the annual median DBD ventilation period for each jurisdiction. † DCD with brain injury as the cause of death.

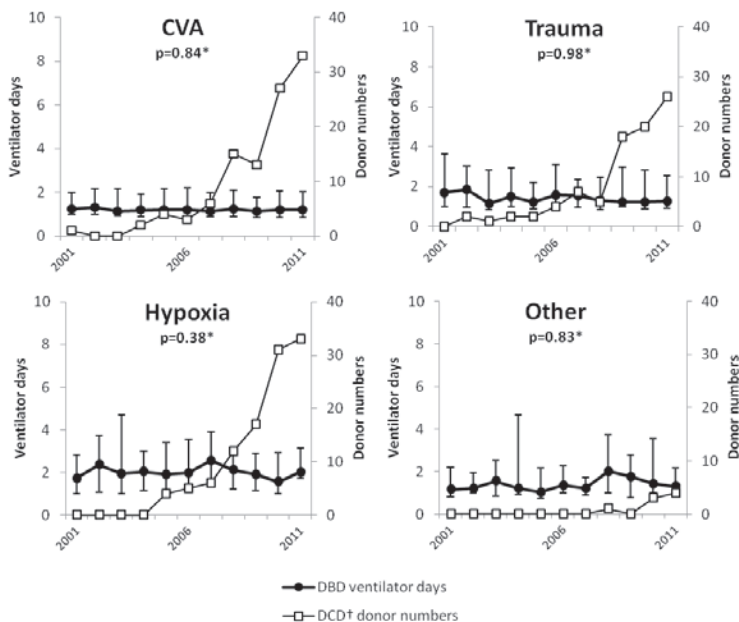
controlled DCD programs, there has been a rise in brain-dead donor numbers over the same period.<sup>11</sup> Brain-dead donor numbers actually increased after the successful introduction of a controlled DCD program in Liege, Belgium,<sup>17</sup> despite a national fall in DBD numbers.<sup>11</sup> Additionally, when donors who received aggressive neurological management were excluded in a single-centre study from the US, there was still a significant rise in DCD.<sup>15</sup>

The findings from these studies suggest that prevention of brain death through the provision of good intensive care is not the only possible explanation for the fall in brain-dead donor numbers. The most plausible alternative explanation is that potential donors are proceeding to DCD before brain death has had time to occur; thereby converting potential brain-dead donors into DCD donors. Distinguishing between these two potential causes of a decreased brain-

death incidence is important. Monitoring for a fall in the ventilation period in brain-dead donors as DCD increases may be one way to achieve this. While we are unlikely to be able to prevent the impact of modern neurointensive care practices on brain death, it may be possible to recognise and prevent DCD occurring prematurely.

In our study, there was a consistently small proportion of DCD donors ventilated for less than 2 days, which was unaffected by increasing DCD numbers. This suggests that early DCD may be appropriate in a small number of patients with non-survivable brain injury. Sometimes it is apparent very early that brain death is unlikely to occur, such as following decompressive craniectomy for traumatic brain injury or stroke. In these patients, early DCD is unlikely to represent a lost potential brain-dead donor. In Australia, uncontrolled DCD following failed resuscitation attempts (Maastricht cate-

**Figure 5. Ventilation period before brain-death determination in brain-dead donors and DCD donor numbers per year, by cause of death, 2001–2011**



DCD = donation after cardiac death (DCD donor numbers are shown as absolute numbers per year). DBD = donation after brain death (DBD ventilator days are shown as medians with interquartile ranges). CVA = cerebrovascular accident. \* Kruskal–Wallis test was used to compare annual median DBD ventilation period for each cause of death. † DCD with brain injury as the cause of death.

gory II)<sup>3</sup> is not currently practised, and therefore does not account for any short ventilation periods in our study.

The higher proportion of DCD donors dying of hypoxic brain injury might be explained by its pathophysiology, the differences in intensive care management received or a combination of both. It is possible that the global insult of hypoxia is more likely than other causes of brain injury to become non-survivable without progressing to brain death.<sup>18</sup> Alternatively, the routine practice of therapeutic hypothermia for hypoxic brain injury in Australian ICUs might be preventing progression to brain death in some patients, leaving DCD as the only option for donation.<sup>19–21</sup> When brain death did occur from hypoxic brain injury, there was a significantly longer period of ventilation before brain death determination. This is likely to be due to a combination of the routine practice of 12–24 hours of therapeutic hypothermia,<sup>19–22</sup> the difficulty in prognostication before 72 hours<sup>23</sup> and the ANZICS recommendation to delay clinical brain-death testing for at least 24 hours in hypoxic brain injury.<sup>1</sup>

This is the first study to use ventilation period as an outcome measure to determine if controlled DCD is reducing the number of potential brain-dead donors. We believe that DBD ventilation period could be developed as a clinical tool

for use by hospitals and jurisdictions to reduce the risk of potential brain-dead donors being converted to DCD. Although our results cannot be readily applied to individual patients, they may provide guidance on the minimum length of time to wait for brain death to occur for different causes of brain injury. These findings could also form the basis of future research into the development of prediction tools for the timing of brain death in individual patients.

There are limitations to our study. Interpretation of the results is limited by the unavoidable smaller sample size in the DCD group. There are factors that could have affected the ventilation period that were not recorded, including the method of brain-death determination (clinical testing versus imaging), neurosurgical interventions and therapeutic hypothermia. There was a potential for selection bias in DCD donors before January 2008 because the ventilation period could only be estimated. However, as DCD numbers increased markedly from 2008 we believe this is unlikely to have had a significant effect. We made assumptions that may not have been correct, including that the initiation of ventilation was an emergent intervention for the brain injury that ultimately led to the patient's death; it is possible that the brain injury occurred sometime after initiation of ventilation, or was initially survivable and subsequently worsened. This may explain the long ventilation period in a small number of patients from both groups. We also assumed that no DCD donor was brain dead; it is possible that some may have met the criteria for brain death but did not have brain-death testing performed. However, we feel it is unlikely that many DCD donors would have had undiagnosed brain death in Australian ICUs.

In conclusion, brain-injured donors in Australia appear to have been ventilated for a long enough period to allow progression to brain death before proceeding to DCD. Therefore, DCD is unlikely to have reduced the brain-dead donor pool.

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### Competing interests

None declared.



## Author details

Brett G Sampson, Intensivist,<sup>1</sup> and Senior Lecturer<sup>2</sup>

Gerry P O'Callaghan, Senior Intensivist,<sup>1</sup> and Senior Lecturer<sup>2</sup>

Graeme R Russ, Chair of Executive, Australian and New Zealand Dialysis and Transplant Registry and Australian and New Zealand Organ Donation Registry,<sup>3</sup> and Clinical Professor<sup>4</sup>

1 Intensive and Critical Care Unit, Flinders Medical Centre, Adelaide, SA, Australia.

2 Flinders University, Adelaide, SA, Australia.

3 Royal Adelaide Hospital, Adelaide, SA, Australia.

4 University of Adelaide, Adelaide, SA, Australia.

Correspondence: Brett.Sampson@health.sa.gov.au

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