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The Implications of the Shift Toward Donation After Circulatory Death in Australia

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Background. In recent years, an increasing number of donor livers are being declined for transplantation in Australia. The aim of this study was to evaluate the impact of donation after cardiac death and other factors associated with organ quality on liver utilization rates in Australia. **Methods.** Data on organ donors who donated at least 1 organ between 2005 and 2014 were obtained from the Australia and New Zealand organ donation registry. Temporal changes in donor characteristics were assessed and a logistical regression analysis was performed to evaluate their association with liver nonuse. **Results.** The number of organ donors increased from 175 in 2005 to 344 in 2014, with overall 19% being donation after cardiac death donors ($P < 0.001$). The percentage of livers deemed unsuitable for transplantation increased from 24% in 2005 to 41% in 2014 ($P < 0.001$). Donation after cardiac death was identified as the most important risk factor for nonuse with an odds ratio of 25.88 (95% confidence interval, 18.84-35.56), $P < 0.001$ followed by donor age, obesity, and diabetes. **Discussion.** This study shows that livers donated after circulatory death are an underused resource in Australia. Better use of these currently available organs would be a highly cost-effective way of reducing waiting list mortality in liver transplantation.

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A shortage of available donors remains a major limiting factor in the field of liver transplantation. Currently in Australia, only 50% of patients with end-stage liver disease on the waiting list receive a life-saving transplant each year. At the same time, 10% of patients die or their condition deteriorates to the point that they are no longer deemed suitable for transplant.¹ In 2008, the Australian Federal Government announced a reform program to increase the number of organ donors. As a result, organ donor rates increased from 12 to 16.1 per million population.² Unfortunately, the number of livers available for transplantation has failed to increase at the

same rate, suggesting that more livers are deemed unsuitable for transplantation.^{1,2}

As well as encouraging the use of extended criteria livers (eg, older donors and steatotic livers) and a drive to maximize splitting of suitable donor livers, one of the main strategies adopted has been the promotion of controlled donation after circulatory death (DCD; Maastricht classification type III³). Currently, 28% of organ donors in Australia are DCD donors, which is low compared to the United Kingdom and the Netherlands, where 40% to 45% of organ donors are DCD.^{2,4,5} Donation after circulatory death lung and kidney programs have been very successful with graft and patient

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survival rates comparable to conventional donation after brain death (DBD) organs.^{6,7} Unfortunately, the experience has not been the same for liver transplantation. Donation after circulatory death livers are more susceptible to ischemia-reperfusion injury and their use has been associated with the development of nonanastomotic biliary strictures in 9% to 31% of recipients.^{8,9} As a result, the percentage of liver nonuse attributable to DCD has increased in the United States from 9% in 2004 to 28% in 2010.¹⁰ It is currently unclear what effect DCD donation has on liver nonuse in Australia.

The aim of this study was to evaluate the impact of DCD and other donor characteristics associated with more marginal donors on liver nonuse in Australia over the past 10 years. The study also aimed to further characterize the DCD donors, declined for transplantation, and to identify whether better selection criteria could potentially improve use in the future.

MATERIALS AND METHODS

Study Population

All adult organ donors in Australia who donated at least 1 organ between January 1, 2005 and January 1, 2015 were included in this study. As these donors had no absolute contraindication for the organ donation process, unsuitability for transplantation was most likely the result of liver-specific reasons. A liver donor was defined as an organ donor from whom the liver was retrieved and subsequently transplanted into a recipient. Deidentified donor data were obtained from the Australia and New Zealand Organ Donor (ANZOD) registry. In 1 Australian jurisdiction, the state of Queensland, approval was obtained from the human research ethics committee of the Princess Alexandra Hospital as well as the University of Queensland to access confidential donor data. This allowed access to donor files when data were incomplete or not available from the organ donor registry.

Data Collection

Donor demographics associated with marginal grafts such as donor age, body mass index (BMI), donation type (DCD or DBD), hepatitis B (hepatitis B surface antigen positive) or hepatitis C infection (hepatitis C virus antibody positive and presence of hepatitis C virus RNA by nucleic acid testing), hypertension, and diabetes mellitus were collected. As donor age was not normally distributed, the following age categories were used: younger than 40, 40 to 49, 50 to 59, and older than 60 years. Body mass index was classified as underweight (<18.5 kg/m²), normal weight (18.5–24.99 kg/m²), overweight (25–29.99 kg/m²), and obese (>30 kg/m²). Liver biopsy results were not included from any of the donors, as it is not routine practice to perform a biopsy and the inclusion of biopsy results of selected donors would bias the results. Owing to incomplete data in the organ donor registry during this period, it was not possible to include liver function test results as a parameter in the main analyses. Instead, a subanalysis was performed of the Queensland state donors (n = 468), where alanine aminotransferase (ALT) was categorized as less than 100 versus greater than 100 U/L, bilirubin as less than 20 versus greater than 20 μmol/L, and γ-glutamyl transferase as less than 40 versus greater than 40 U/L.

Additional factors that potentially influence the decision to use a liver for donation such as sex, blood group, presence of hepatitis B core antibody, year of organ retrieval, state of

organ retrieval, cause of death, and smoking status were also recorded. If a donor was identified as a DCD donor, warm ischemic time (WIT) before the start of cold perfusion was recorded. The start of this period was marked by a systolic blood pressure lower than 50 mm Hg or oxygen saturation lower than 50%, whichever occurred first, as per national guidelines.¹¹ In Australia, livers from DCD donors are considered for transplantation if the warm ischemic time is limited to 30 minutes and if they do not have any other extended criteria beyond DCD.¹² From every donor, data on the organs retrieved and whether they were used or discarded was recorded (kidneys, liver, lung, heart, and pancreas). Lastly, from all donors in the State of Queensland, the distance between donor and recipient hospital was recorded. The state area comprises 1,727,000 km², with the liver transplantation center located in the far southeast corner approximately 1700 km from the furthest donor hospital. For the purpose of this study, travel distance was defined as metropolitan (<100 km) and nonmetropolitan (>100 km). Overall, each variable of interest was available from more than 95% of organ donors unless stated otherwise.

Characterization of DCD Nonliver Donors in the State of Queensland

Although the reason for organ nonuse was generally recorded in the organ donor registry, it was found to provide insufficient detailed information especially for DCD donors. We therefore reviewed the donor files of DCD donors in the state of Queensland, and the reason for liver nonuse was recorded.

Statistical Analysis

All continuous variables are expressed as median (interquartile range) and all categorical variables as frequency (percentage). A χ^2 test was performed to compare categorical variables, whereas a Mann-Whitney *U* test was used to compare all continuous variables. A multivariable logistical regression analysis was performed to identify donor characteristics associated with liver nonuse controlled for all factors with $P < 0.1$ in univariable analysis.

A subanalysis was performed on all Queensland donors to assess the association between donor hospital distance, abnormal liver function tests, and liver nonuse. The statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 23.0 (IBM Corp, IBM SPSS statistics, Armonk, NY) and a *P* value of less than 0.05 was considered significant.

RESULTS

Donor Characteristics

Between 2005 and 2014, a total of 2547 organ donors in Australia were identified who donated at least a single organ (Table 1). Of these, most organ donors were Caucasian (93%) and 55% were men. In addition, 706 (28%) were older than 60 years, 470 (19%) were DCD, and 957 (38%) and 623 (25%) were overweight or obese, respectively. Only a very small proportion of organ donors tested positive for hepatitis B or hepatitis C (0.3% and 1%, respectively), 8% were diabetic, and 27% had a history of hypertension. Stroke was the most common cause of death (54%) followed by hypoxia. The median number of organs transplanted per donor was 3. Most of the organ donors donated 1 or both kidneys (94%) followed by liver (65%), lung (43%), pancreas (32%), and heart (28%).

TABLE 1.**Donor characteristics between 2005 and 2014**

Characteristic	2005 (N = 175)	2014 (N = 344)	Overall (N = 2547)	P
Age, yrs	47 (36-56)	51 (40-60)	50 (37-60)	0.008
Sex, male	91 (52%)	188 (55%)	1401 (55%)	0.5
Race, Caucasian	164 (94%)	307 (89%)	2359 (93%)	0.1
Body mass index, kg/m ²	26 (24-29)	27 (24-30)	26 (24-30)	0.5
Donor type (DBD)	167 (95%)	249 (72%)	2077 (82%)	<0.001
Cause of death				
Stroke	106 (61%)	174 (51%)	1363 (54%)	<0.001
Hypoxia	17 (10%)	99 (29%)	517 (20%)	
Accident	28 (16%)	48 (14%)	402 (16%)	
Other	24 (14%)	23 (7%)	265 (10%)	
Diabetes mellitus	13 (7%)	22 (6%)	205 (8%)	0.7
Hypertension	44 (25%)	96 (28%)	687 (27%)	0.5
Smoking				0.01
Current	62 (35%)	152 (44%)	9030 (40%)	
Never	81 (46%)	109 (32%)	910 (36%)	
Former	32 (18%)	83 (24%)	601 (24%)	
Hepatitis B core antibody	11 (6%)	18 (5%)	130 (5%)	0.02
Hepatitis B surface antigen	0 (0%)	5 (2%)	7 (0.3%)	0.2
Hepatitis C antibody + HCV RNA	3 (2%)	2 (1%)	21 (1%)	0.2
WIT ^a , min	Data not available	23 (20-28)	22 (18-27)	–
ALT ^b , U/L	28 (16-85)	42 (23-68)	38 (22-69)	0.5
Bilirubin ^b , μmol/L	13 (7-16)	13 (9-18)	12 (8-17)	0.4
Gamma-GT ^b (U/L)	41 (22-75)	32 (19-59)	42 (23-70)	0.4
Distance donor hospital ^b , km	8 (0-492)	67 (8-798)	40 (6-291)	0.2
Number of organs retrieved and transplanted	4 (3-5)	3 (2-4)	3 (3-5)	<0.001

^a Available from 387 (82%) of DCD donors.

^b The data presented here are from the Queensland state donor subgroup only. N = 468.

Because of rounding, not all percentages add up to 100%.

P values indicates statistically significant.

HCV, hepatitis C virus.

Changes in Donor Characteristics Over Time

Over the 10-year study period, the number of organ donors per year almost doubled from 175 in 2005 to 344 in 2014 (Figure 1). Since 2008, there has been a steady increase in the number of DCD organ donors, with 28% of all organs donated being from a DCD donor in 2014. In 2005, the percentage of organ donors younger than 40 years was 30%, which decreased to 24% in 2014. In contrast, the proportion of organ donors older than 60 increased by 10%. During the study period, the proportion of overweight and obese donors remained stable with a median BMI of 26 kg/m² (24-30 kg/m²). More donors were current or former smokers or died from hypoxic injury in 2014, compared with 2005 (Table 1). Overall, the median number of organs retrieved and transplanted per donor decreased from 4 (3-5) in 2005 to 3 (2-4) in 2014 ($P < 0.001$). Among Queensland state organ donors, the median ALT, bilirubin, and γ -glutamyl transferase values did not change over the 10-year study period, with 75 organ donors (16%) having an ALT of greater than 100 U/L.

Temporal Trends in Liver Nonuse

Overall, a liver was retrieved and subsequently transplanted from 1643 organ donors (65%). Over time, the proportion of livers deemed unsuitable for transplantation from DBD donors remained stable between 20% and 30% (Figure 2). Since 2005, only 64 DCD livers (14%) were used for transplantation. Over the 10-year study period, the percentage

of DCD livers rejected for transplantation was between 80% and 100% on an annual basis. As the proportion of DCD donors has increased over time, the overall number of livers not used for transplantation increased from 42 (24%) in 2005 to 141 (41%) in 2014 ($P < 0.001$).

Risk Factors for Liver Nonuse

In univariable analysis, liver nonuse was strongly associated with DCD donor type ($P < 0.001$; Table 2). Furthermore, livers from older donors and overweight or obese donors were less likely to be used. Organs from donors who died from hypoxia, compared to those who suffered a stroke, were more likely to be declined for transplant. In addition, liver nonuse was associated with donors who were former smokers, compared to those who did not smoke. The presence of hypertension and diabetes in the donor population was also associated with liver nonuse. In the subgroup of 468 DCD donors, a WIT of more than 20 minutes was associated with liver nonuse (odds ratio [OR], 3.05 [95% confidence interval [CI], 1.70-5.49], $P < 0.001$). In univariable analysis of Queensland state organ donors, ALT concentration of greater than 100 U/L and γ -glutamyl transferase greater than 40 U/L were associated with liver nonuse (OR, 3.01 [95% CI, 1.81-4.99], $P < 0.001$ and OR, 13.30 [95% CI, 7.99-22.12], $P < 0.001$, respectively).

In multivariable analysis, DCD donor type was identified as the most significant independent risk factor for liver nonuse

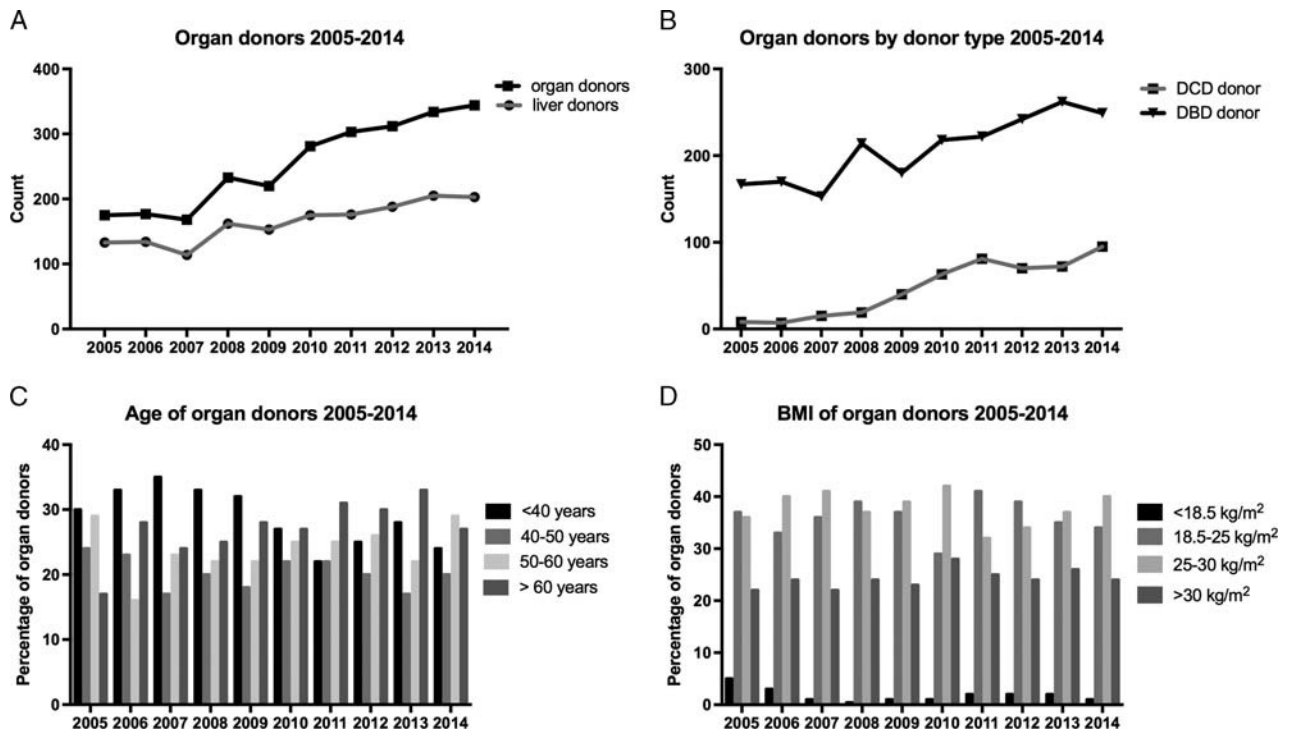


FIGURE 1. Changing organ donor characteristics between 2005 and 2014. A, Increase in the number of organ donors and organ donors donating their liver (liver donors) between 2005 and 2014. B, Number of livers donated after circulatory death (DCD) and donated after brain death (DBD) between 2005 and 2014. C, Age of organ donors between 2005 and 2014. D, Body mass index (BMI, kg/m²) of organ donors between 2005 and 2014.

with an OR of 25.88 (95% CI, 18.84-35.56) ($P < 0.001$; Table 2). Furthermore, donor age older than 40 years was associated with liver nonuse with livers from donors older than 60 years being the least likely to be used (OR, 3.66 [95% CI, 2.62-5.11], $P < 0.001$). Donor obesity was also associated with higher odds for nonuse ($P < 0.001$) as was diabetes. In the Queensland state organ donor subset, ALT greater than 100 U/L and γ -glutamyl transferase greater than 40 U/L were strongly associated with nonuse (OR, 4.99 [95% CI, 2.23-11.19], $P < 0.001$ and OR, 12.21 [95% CI, 6.20-24.02], $P < 0.001$, respectively).

Characteristics of DCD Nonliver Donors in the State of Queensland

Since 2008, there were 91 DCD organ donors in the state of Queensland, but only 10 livers retrieved from these donors were used for transplantation. Compared to DBD donors, DCD donors were more often in the metropolitan area (88% vs 65%, $P < 0.001$). Most of the DCD nonliver donors (85%) had a WIT of less than 30 minutes and 27 (33%) had recorded a WIT less than 20 minutes. Furthermore, 36 nonliver donors (44%) were younger than 50 years, and 16 (44%) of those had a normal BMI.

Donor chart analysis showed that before mid-2011, no active DCD liver transplant program was in place. From 2011 onward, the main reason DCD livers were not used for transplantation was donor age (33 [41%]; Figure 3). Other reasons were medical suitability (6 [7%], eg, ischemic damage to the liver), logistics (4 [5%], eg, 2 concurrent donors) and no suitable recipient (2 [2%], eg, no recipient with the correct blood group).

DISCUSSION

In recent years, DCD donors have been identified as a potential source to increase donor numbers. The use of lungs and kidneys donated after circulatory death have been widely adopted in Australia.^{13,14} More recently, the first successful transplant of a normothermally perfused DCD heart was performed by our colleagues at St Vincent's Hospital in Sydney.¹⁵ Unfortunately, the experience with DCD donor livers is rather different. Although the number of organ donors and the number of liver donors substantially increased over the study period, a greater proportion of livers were

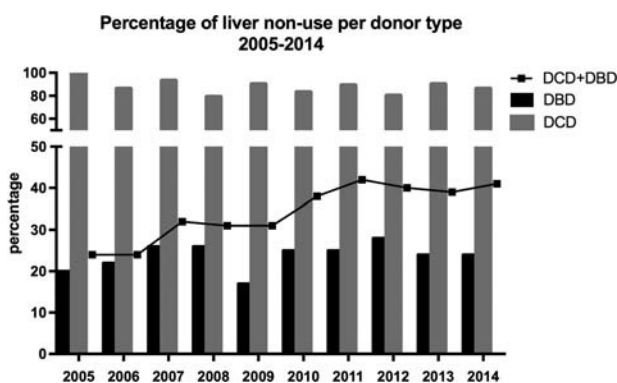


FIGURE 2. Increased percentage of liver nonuse between 2005 and 2014. This graph shows DCD (gray bars) and DBD (black bars) nonliver donors as a percentage of all organ donors from the corresponding donor type. The black line represents the overall percentage of livers not used for transplantation when the 2 donor types were combined.

TABLE 2.
Donor characteristics associated with liver nonuse

Characteristic	Univariable regression		Multivariable regression ^a	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (vs < 40), yrs				
40-50	1.64 (1.28-2.11)	<0.001	1.67 (1.21-2.33)	0.002
50-60	2.26 (1.79-2.87)	<0.001	2.34 (1.70-3.22)	<0.001
> 60	2.75 (2.19-3.46)	<0.001	3.66 (2.62-5.11)	<0.001
BMI (vs 18.5-24.99), kg/m ²				
< 18.5	1.46 (0.79-2.68)	0.2	1.81 (0.87-3.77)	0.1
25-29.99	1.33 (1.09-1.62)	0.005	1.28 (0.99-1.64)	0.06
> 30	2.58 (2.23-3.41)	<0.001	3.02 (2.31-3.95)	<0.001
Donor type (DCD)	20.11 (15.17-26.67)	<0.001	25.88 (18.84-35.56)	<0.001
Cause of death (vs stroke)				
Hypoxia	1.75 (1.43-2.15)	<0.001	1.33 (1.00-1.76)	0.05
Accident	0.95 (0.74-1.20)	0.6	0.99 (0.71-1.37)	0.9
Other	0.75 (0.72-1.27)	0.7	1.08 (0.74-1.58)	0.7
Hypertension	1.63 (1.36-1.95)	<0.001	1.19 (0.93-1.52)	0.2
Diabetes mellitus	1.74 (1.31-2.32)	<0.001	1.61 (1.13-2.27)	0.008
Smoking (vs never)				
Current	0.73 (0.60-0.88)	0.001	0.83 (0.65-1.05)	0.1
Former	1.16 (0.94-1.43)	0.2	0.97 (0.74-1.25)	0.8
Hepatitis B core antibody	1.11 (0.77-1.60)	0.6		
Hepatitis B surface antigen	4.57 (0.88-23.58)	0.07	2.59 (0.43-15.56)	0.3
Hepatitis C antibody + HCV RNA	0.57 (0.21-1.55)	0.3		

^aAll factors with $P < 0.1$ in univariable regression analysis as well as ABO blood group, donor state, year (continuous), race, and sex were included in the multivariable regression model. P values indicates statistically significant.

deemed unsuitable for transplantation. This was associated with an increase in DCD livers, which were not accepted for transplantation.

The decreasing rate of liver use is a pressing problem around the globe. In the United Kingdom, the proportion of livers used for transplantation has dropped from 79% (n = 601) in 2005-2006 to 63% (n = 812) in 2014-2015.^{5,16} Furthermore, Osman et al¹⁰ found that in the United States, liver nonuse increased from 15% in 2004 to 21% in 2010, with DCD as the most important risk factor (OR, 21.31 [95% CI, 18.30-24.81]). The present study indicates that liver nonuse is an even bigger problem in Australia, as the proportion of DCD donors in the total cohort is higher. Australian centers have had a conservative approach to the use of DCD livers

because a small population (24 million) limits access to emergency retransplantation in the event of primary nonfunction. Therefore, livers from DCD donors are rarely considered for transplantation if they are older than 40 to 45 years, in an attempt to select more superior grafts.¹² This despite favorable outcomes of the use of older DCD donors reported in the United Kingdom and the Netherlands.^{9,17,18}

One of the most important questions currently is whether some DCD donors, if given the time, would in fact progress to brain death.¹⁹ If so, this would mean that a proportion of DBD organ donors, with expected good organ quality, were converted into the less favorable DCD type, which the present study shows is associated with high odds of liver nonuse. Reasons for this conversion could be that the DCD donation process is easier to comprehend by donor families and they prefer to accompany their family member until cardiac arrest has occurred.²⁰ Furthermore, bed capacity in the intensive care unit could put pressure on the time-consuming neurological observations required to medically and legally determine brain death. A recent study assessing transplant rates in 82 countries showed that between 2000 and 2010, countries with high DCD rates had declining or static DBD rates.¹⁹ Furthermore, this study by Bendorf et al showed that the increase in the number of DBD donors, and not DCD, was the basis of higher sustained donation rates of more than 20 per million population in countries such as Spain, France, and the United States. Taken together, this might indicate that the focus needs to shift back to increasing the number of DBD donors.

To facilitate the use of high-risk donors such as DCD, risk factors such as WIT, cold ischemic time, and distance traveled need to be modified. Currently in Australia, withdrawal of life support takes place in the intensive care unit. After cessation

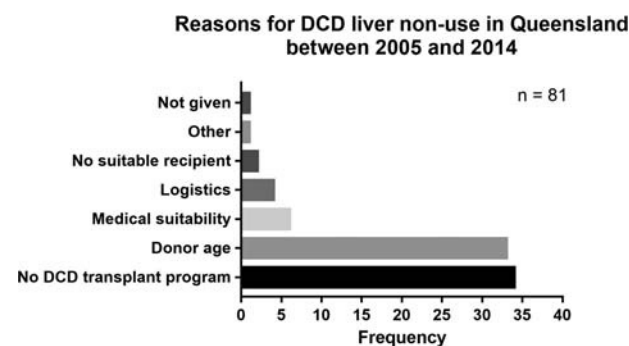


FIGURE 3. Reasons for DCD liver nonuse in Queensland between 2005 and 2014. This graph provides the reasons why DCD livers were not used for transplantation. After the introduction of a DCD liver transplant program in 2011, DCD livers were not used because of donor age (n = 33), medical suitability (n = 6), logistics (n = 4), no suitable recipient (n = 2), other (n = 1), and not given (n = 1).

of circulation, a legally obligated 5-minute stand down period is in place to make sure that autoresuscitation does not occur. The organ donor is then brought into the operating room, which can take 3 to 4 minutes. Withdrawal of life support in the operating room would significantly expedite the process and reduce WIT. Cold ischaemic time in Australia is largely dependent on travel time due to the long distances. Although actual flying times to distant parts of the state may only take 3 to 4 hours, ground transport between hospitals and airport has to be taken into account. Additional staff at the donor hospital (eg, donation specialist nurse) to care for the donor once organ retrieval is finalized could facilitate a quicker departure. This approach has been implemented in the larger nonmetropolitan hospitals throughout Australia. Furthermore, police escorts to and from the airport could significantly reduce travel time, especially during peak hour. Unfortunately, this is not possible in most states. By far the most effective way to reduce travel time is to focus on metropolitan donors only. This approach has facilitated the use of more high-risk donors in other countries such as Canada.²¹

Nevertheless, the biggest challenge to date is to build the confidence among transplant surgeons and physicians that the use of DCD donor livers can be safe. Despite the favorable graft and patient survival of DCD liver transplant programs in the United Kingdom and The Netherlands,^{8,9} even those DCD grafts that fulfill the current acceptance criteria in our cohort were not used for transplantation. Unfortunately, we were unable to determine the exact reasons for this.

The use of alternative preservation methods such as machine perfusion could be the solution to facilitate the use of DCD donor livers for transplantation.²² Machine perfusion reduces the preservation injury and therefore holds the potential to better preserve organ quality and possibly even rescue marginal donors who are outside current criteria (eg, DCD donor organs with WIT >30 minutes and macrovesicular steatosis >30%).²³⁻²⁵ Machine perfusion furthermore opens up the possibility for organ sharing and use of marginal donors between geographically distant centers in Australia as preservation periods could be extended. Lastly, normothermic machine perfusion allows for assessment of viability, an important tool to avoid transplanting a liver that would in fact fail to function.²⁶ The ability to directly assess liver function may offer a rational alternative to the use of current empirical criteria for selection of DCD livers for transplantation.

As the application of machine perfusion is still an upcoming new technique, it is difficult to predict what the impact would be on the overall number of livers available for transplantation. Sutton et al estimated that 50% of the discarded extended criteria livers (DCD, 10; DBD, 2) they perfused showed signs of good organ function.²⁷ Furthermore, based on results of a pilot series, Mergental et al estimated a potential increase in the number of liver grafts in the United Kingdom by 15% if 70% of currently declined extended criteria livers could be used.²⁸

The limitations of the study arise mainly from its retrospective nature. The reasons for nonuse of each organ are registered in the nationwide database, but in most cases, this was not well defined (eg, 'medical unsuitability' or DCD). Furthermore, no histological data were available to determine the impact of hepatic steatosis. Obesity and diabetes mellitus were however included in the cohort, and these factors are strongly associated with hepatic steatosis.²⁹ Finally,

it was only possible to assess the impact of abnormal liver function tests and donor hospital location in the Queensland state donor cohort. As this cohort only comprised 18% of all Australian organ donors, it might not represent the entire study cohort.

Despite these limitations, this study shows that livers donated after circulatory death are an underused resource in Australia. Better use of these currently available organs would be a highly cost-effective way of reducing waiting list mortality in liver transplantation.

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