Brain Death Donors on Extracorporeal Membrane Oxygenation Support

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Abstract

Objectives: **We investigated donors with brain death on extracorporeal membrane oxygenation support, a clinically challenging situation due to hemodynamic instability frequently encountered in these donors, which may threaten organ function.**

Materials and Methods: **We described our experience with 15 utilized brain death donors on extracorporeal membrane oxygenation support, consecutively admitted in our intensive care unit (which is a referral center for extracorporeal membrane oxygenation) from 2018 to 2023. We investigated whether utilization rate for brain death donors on extracor-poreal membrane oxygenation was affected by the introduction of a monitoring hemodynamic schedule during the 6-hour observation period.**

Results: **The utilization rate was 78% in period 1 and 88% in period 2. No statistically significant differences were observed for age, sex, and the incidence of cardiovascular risk factors between period 1 and period 2. The cause of death was postanoxic encephalopathy in all but 1 donor, who was on venovenous extracorporeal membrane oxygenation for refractory respiratory failure and developed cerebral hemorrhage. Number of organs per donor was 2 in all the population with no significant differences between period 1 and period 2. In the overall population, 15 livers were transplanted, 11 kidneys, 1 heart, and 1 pancreas. In our population, left ventricular ejection fraction severe dysfunction was observed in all donors except in the donor on venovenous extracorporeal membrane oxygenation; the organ from this donor was deemed unsuitable for transplant. No significant differences were observed in hemodynamic data between the 2 subgroups. All donors were on 2 vasoactive drugs (norepinephrine and vasopressin) to maintain adequate perfusion (mean arterial pressure >60 mm Hg). Three donors were oligoanuric (due to postarrest acute renal failure).**

Conclusions: **In our series of 15 consecutive brain death donors on extracorporeal membrane oxygenation, a strict monitoring regimen during the 6-hour observation period was associated with a higher utilization rate.**

Key words: *Allocation policy, Hemodynamic monitoring, Utilized donors*

Introduction

Extracorporeal membrane oxygenation (ECMO) is an established support therapy for patients with cardiac and/or respiratory failure refractory to standard therapy. In the past decade, an exceptional increase in ECMO utilization was observed worldwide.[1,2] Adult extracorporeal cardiopulmonary resuscitation (ECPR) is increasingly used to treat refractory out-of-hospital cardiac arrest,[3] the annual incidence of which has been estimated at 50 to 74 per 100 000 population.[4] The prevalence of brain death was significantly higher in patients resuscitated with ECPR compared with patients resuscitated with conventional CPR (27.9% [range 19.7%-36.6%] vs 8.3% [range 6.5%-10.4%], respectively; $P < .0001$).[5] We recently reported 134 cases of out-of-hospital cardiac arrest (June 2016 to December 2018) with no return of spontaneous circulation, for which ECPR was implanted in 26 patients (26 of 86, 30%). Among these patients, 8 patients evolved in brain death and became donors (8 of 34, 33%).[6]

The situation of DBD on ECMO support represents a clinical challenge due to hemodynamic instability frequently encountered in these donors, which may threaten organ function. To date, few data

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are available regarding DBD on ECMO support, including heterogenous population (adult and pediatric donors), and most previous investigations have focused on graft outcomes.[7-10]

We described our experience with 15 utilized DBD on ECMO support, consecutively admitted for the period 2018 to 2023 in our intensive care unit (ICU), which is a referral center for ECMO support. We investigated whether utilization rate in DBD on ECMO was affected by the new hemodynamic monitoring schedule during the 6-hour observation period, as introduced by the Tuscany Transplant Authority in 2019.

Materials and Methods

In the present case series, we enrolled 25 DBD on ECMO consecutively admitted to our ICU from January 1, 2018, to December 31, 2023. The study population comprised 15 utilized DBD on ECMO. Two periods were considered: period 1 (2018 to 2020) and period 2 (2021 to 2023). These 2 periods were chosen with regard to a hemodynamic monitoring schedule during the 6-hour observation period, as mandated by the Tuscany Transplant Authority.

Study population

Diagnosis of death was confirmed by strict adherence to standardized clinical, neurologic, and electroencephalogram criteria in accordance with the Italian law and related guidelines. According to the Italian law, death by neurologic criteria may be certified after a 6-hour observation period.

Clinical data included age, sex, risk factors (hypertension, diabetes mellitus, and known previous coronary artery disease), and cause of death. Data were prospectively recorded and retrospectively analyzed.

Donor treatment

All potential donors were treated as previously described.[11,12] Hemodynamic management also included replacement therapy with cortisone and thyroid hormone.[13] Antidiuretic hormone and intravenous insulin (target glucose values <180 mg/dL) were considered on a case-by-case basis.

In 2019 the Tuscany Transplant Authority implemented the use of a hemodynamic monitoring schedule in which systolic and diastolic blood pressures, heart rate, central venous pressure, and diuresis were reported by the transplant coordinator during the 6-hour observation period. In DBD on ECMO support, blood flows were also monitored and maintained at a level of at least 3 L/min.

In the presence of a reduction in blood pressure, the following changes were made according to our protocol: (1) volume replacement (crystalloid) whenever a reduction in mean arterial pressure (MAP) was observed and (2) increase in norepinephrine dose up to 0.2 μg/kg/min. If this norepinephrine dosage is not sufficient to restore perfusion (MAP >60 mm Hg), then vasopressin is added. Hemodynamic data were reported at the beginning (time 1) and the end of the observation period (time 2).

Echocardiography was performed by a cardiologist (CL, MB) in all donors according to our local protocol.[14] Echocardiography sessions were performed at the beginning (time 1) and the end of the observation period (time 2), and the left ventricular ejection fraction (LVEF) was reported.

Statistical analyses

Data were analyzed with the use of SPSS statistical software (version 20). A 2-tailed $P < .05$ was considered statistically significant. Categorical variables are reported as frequencies and percentages, and continuous variables are reported as the mean ± SD or median (and 25th-75th IQR). For continuous variables, between-group comparisons were made using analysis of variance (followed by Bonferroni posttests if the overall P value was significant) or by the Kruskal-Wallis H test. Categorical variables were compared by chi-square tests.

Results

Our population included 25 consecutive DBD on ECMO support. Table 1 shows the number of DBD admitted to our ICU during the study period. One donor was on venovenous ECMO per refractory respiratory failure due to bacterial pneumonia; the remaining 24 DBD were on ECMO support due to refractory cardiac arrest. The etiology of cardiac arrest was acute coronary syndrome in 23 DBD and previously known dilated cardiomyopathy in 1 DBD.

The number of DBD did not differ between the 2 periods ($P = .129$), and the percentage of DBD on ECMO support was comparable between the 2

periods ($P = .511$). In period 1, among the 14 DBD on ECMO, no family refusal was observed, but organs from 5 donors were not considered for transplant in the operating room. The utilization rate was 78% in period 1. During period 2, family refusal was present in 3 cases, and the organ from 1 donor was deemed ineligible for transplant. The utilization rate in period 2 was 88%.

Table 2 shows the clinical characteristics of the utilized DBD on ECMO (the study population). No significant differences were observed in age, sex, and the incidence of cardiovascular risk factors between period 1 and period 2. The cause of death was postanoxic encephalopathy in all but 1 donor, who was on venovenous ECMO for refractory respiratory failure and developed cerebral hemorrhage. The number of organs per donor was 2 in all the population with no significant differences between period 1 and period 2. In the overall population, 15 livers were transplanted, 11 kidneys, 1 heart, and 1 pancreas.

Table 1. Study Population

	Period 1 (2018-2020)	Period 2 (2021-2023)	*P*
All DBD, No. of donors	119	120	.129[a]
Utilized DBD, No. of donors	63	54	
DBD on ECMO, No. of donors (%)	14 (11%)	11 (9.2%)	.511[a]
Utilized DBD on ECMO, No. of donors	7	8	

Abbreviations: DBD, donation after brain death; ECMO, extracorporeal membrane oxygenation
[a]Chi-square test

Table 2. Utilized Donation After Brain Death on Extracorporeal Membrane Oxygenation

	All	Period 1 (2018-2020)	Period 2 (2021-2023)	*P*
No. of donors (%)	15	7 (30%)	8 (70%)	
Age, mean ± SD, y	49 ± 8	44 ± 8	51 ± 8	.115[b]
Males, No. (%)	11 (74%)	5 (71%)	6 (75%)	.875[a]
Risk factor, No. (%)				.727[a]
Hypertension	5 (33%)	1	4	
Diabetes	3 (20%)	1	2	
Heart disease	1 (7%)	1	0	
Cause of death, No. (%)				.002[a]
Stroke	1 (7%)	1	0	
Postanoxic encephalopathy	14 (93%)	6	8	
Organ per donor	2	2.1	1.7	

[a]Chi-square test. [b]Student *t* test.

Table 3 depicts hemodynamic data recorded at the beginning and at the end of the 6-hour observation period in all utilized DBD on ECMO. Data were compared between period 1 and period 2.

In our population, LVEF severe dysfunction was observed in all donors except in the donor on venovenous ECMO. In this donor, the heart was deemed unsuitable for transplant. No significant differences were observed in hemodynamic data between the 2 subgroups. All donors were on 2 vasoactive drugs (norepinephrine and vasopressin) to maintain adequate perfusion (MAP >60 mm Hg). Three donors were oligoanuric (due to postarrest acute renal failure).

Table 3. Hemodynamic Data

	Period 1 (2018-2020)	Period 2 (2021-2023)	*P*
Time 1			
LVEF, % (range)	26.2 (15-55)	21 (14-23)	.785[b]
MAP, mean ± SD, mm Hg	63 ± 7	63 ± 9	.887[b]
HR, mean ± SD, beats/min	93 ± 12	86 ± 20	.418[b]
NE, %	100	100	
NE dose, median (range), µg/kg/min	0.45 (0.1-6)	0.5 (0.2-1.2)	.885[a]
Other vasoactive agents, %	100%	100%	
Urine output, median (range)	80 (1-200)	140 (80-250)	.494[a]
Lactate, median (range), mg/dL	3 (1.3-4)	3 (0.6-8.7)	.947[a]
Blood flow, L/min	3 (2.6-3.3)	2.8 (2.1-3.9)	.897[a]
Time 2			
LVEF, % (range)	27 (15-50)	22 (16-27)	.728[b]
MAP, mean ± SD, mm Hg	55 ± 10	64 ± 9	.089[b]
HR, mean ± SD, beats/min	92 ± 12	88 ± 18	.626[b]
NE, %	100	100	
NE dose, median (range), µg/kg/min	0.45 (0.1-6)	0.4 (0.2-1.1)	.885[a]
Other vasoactive agents, %	100	100	
Urine output, median (range)	100 (1-180)	150 (90-220)	.494[a]
Lactate, median (range), mg/dL	3 (1.2-4.1)	2 (1.3-8.9)	.947[a]
Blood flow, L/min	3 (2.2-3.2)	2.8 (2-3)	.953[a]

Abbreviations: HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NE, norepinephrine
[a]Analysis of variance. [b]Student *t* test.

Discussion

The main finding of our investigation performed in a series of 15 consecutive DBD on ECMO showed that a strict monitoring regimen during the 6-hour observation period was associated with an increase in utilization rate.

Few data are available for DBD on ECMO support, and most previous studies have focused on graft outcomes. In a retrospective investigation (2016-2020), Fainberg and colleagues[7] assessed the percentage of donors among patients on ECMO support and documented that one-third of patients referred to the organ procurement organization donated organs. The authors concluded that clinicians should not consider ECMO to be a barrier to organ donation. The population assessed by Fainberg and colleagues[7] was quite different from the population in our study. In their study,[7] both adult and pediatric patients were included, and the population

comprised both DBD (5%) and donation after circulatory death (49%). Results by Fainberg and colleagues[7] are therefore incomparable with results from our study, although in their series, the number of DBD on ECMO was comparable with our study (20 vs 15). Unfortunately, the subgroup of DBD on ECMO was not specifically investigated by Fainberg and colleagues.[7] Data regarding outcomes of organs transplanted from patients on ECMO are sparse.

Bronchard and colleagues[8] found similar graft function and recipient survival when organs were recovered from patients on ECMO compared with patients not on ECMO at the time of death. The authors focused on kidney graft outcome.[8] Carter and colleagues[9] assessed graft survival of kidneys and livers, but their population, unlike ours, comprised DBD and donation after circulatory death.

The novelty of our investigation is that we specifically assessed hemodynamic management in DBD on ECMO support. In these donors, difficulties in maintaining adequate systemic perfusion are related mainly to 3 factors. The first factor is represented by all systemic cardiovascular derangement following brain death, including systemic vasoconstriction followed by vasodilatation and inflammatory activation. The second factor is that ECMO support is associated with continuous flow, and no data are yet available regarding the lack of the pulsatile component of blood flow in organ perfusion in DBD. The coexis-tence of severe LVEF dysfunction, as observed in our population, indicates that ECMO-induced continuous flow is the main contributor to systemic organ perfusion. Finally, patients with brain death after successful resuscitation after cardiac arrest[5] show features of the so-called postresuscitated cardiac syndrome (frequently in its early and intermediate phases), which is mainly characterized by myocardial dysfunction and systemic ischemia/reperfusion response. The latter causes activation of immunologic and coagulation pathways, which increase the risk of organ failure and infection.

In transplantation medicine, the time frame between the time of brain death diagnosis (in Italy, it is the 6-hour observation period) and referral to the operating room for procurement should be viewed as an opportunity to optimize DBD treatment and improve organ quality.

In this context, our finding of an increased utilization rate after the introduction of a strict monitoring schedule strongly supports the notion that in DBD on ECMO support an accurate hemodynamic monitoring regimen and well-defined local protocols for donor management are crucial for maintaining organ perfusion and quality for transplant. According to our experience, an allocation policy that establishes a brief (<3 h) time for organ retrieval following the end of the observation period may have contributed to the increased utilization rate observed in our series.

Study limitations

A potential limitation of our study may be the small number of DBD on ECMO. However, this is a case series of consecutive donors treated by the same ICU team, following local protocols in a center with a high volume of DBD. Graft outcomes were not investigated in our study, because our aim was to assess the effect of a strict hemodynamic monitoring regimen in these donors.

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