



Epidemiological changes in potential heart donors after brain death: a retrospective 15 year cohort study

Adriano Peris^{1,2}  · Chiara Lazzeri¹ · Lorenzo D'Antonio² · Marco Bombardi² · Manuela Bonizzoli¹ · Cristiana Guetti¹ · Massimo Maccherini³ · Maria Luisa Migliaccio²

Received: 10 April 2018 / Accepted: 15 June 2018 / Published online: 26 June 2018
© SIMI 2018

Abstract

Changes in the causes of brain death may influence the numbers of hearts that can be procured and transplanted. We retrospectively investigated whether the distribution of causes responsible for brain death have changed over a 15-year period in a cohort of 1286 potential heart donor (aged ≤ 60), and whether it influenced heart procurement. Between 2001 and 2016, the age of potential donors significantly increased ($p < 0.0001$) as well as the relative proportion of postanoxic brain death, while that of traumatic brain injury decreased ($p = 0.0007$). A significant increase in the use of norepinephrine was detectable. The number of transplanted hearts did not significantly change, with no differences in the age of donors or in the causes of brain death. According to our data, in our 15-year study period, significant changes in the causes of brain death occurred (indicated by a reduction in potential donors following traumatic brain injury) together with an increase in donor age. Nevertheless, the number of transplanted hearts did not change probably thanks to a modified donor management (as inferred by a different use of vasoactive drugs).

Keywords Causes of brain death · Transplantation system · Potential heart donor · Heart procurement

Introduction

Brain death remains the most common source of organs for transplantation worldwide, and the cause of brain injury may influence the numbers of hearts that can be procured and transplanted. Epidemiological changes in the distribution of causes of brain death in organ donors were reported in previous investigations performed in Canada [1], United States [2, 3] and in Belgium [4, 5]. In these countries, a relative decline in the proportion of donors with traumatic brain injury, and an increase in those with anoxic brain injury, was reported. So far, this issue has not been specifically addressed in Italy and in potential heart donors (that is ≤ 60 years).

Therefore, we retrospectively investigated whether the distribution of causes responsible for brain death has changed over a 15-year period in a cohort of 1286 potential heart donor (aged ≤ 60), and, if so, whether it influenced heart procurement in the Tuscany Region.

Methods

In a retrospective analysis, we included brain dead donors aged ≤ 60 years in Tuscany Region (about 3.6 million residents) from 2001 to 2016. During this time frame, we compared two different periods: period 1, 2001–2008 and period 2, 2009–2016. The choice of these two periods was carried out on the basis of the organizational transformation of the Tuscany Authorities for Transplantation, initially as “programmatic organ” (2001–2008) until the full application of clinical governance (2009–2016).

Diagnosis of death was confirmed by strict adherence to standardized clinical, neurological and EEG criteria in accordance with Italian law, (clinical and neurological criteria, confirmed by EEG after 6-h observation by an independent

✉ Adriano Peris
aperis@libero.it

¹ Emergency Department, Intensive Care Unit and Regional ECMO Referral Centre, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 1, 50134 Florence, Italy

² Tuscany Authority for Transplantation (Centro Regionale Allocazione Organi e Tessuti CRAOT), Florence, Italy

³ Department of Cardiovascular Diseases, University of Siena, Siena, Italy

committee of three specialists) and related guidelines. Data were prospectively recorded and retrospectively analysed.

The study was approved by the Institutional Review Board of Regional Authority for Transplantation, and it is in accordance with Helsinki Declaration of 1975.

The purpose of this study is to document changes induced in heart transplantation as a result of changes in the etiology of encephalic death over the years. In addition, the Transplantation Organization in Italy provides for the allocation of the heart throughout the Italian national network, with the possibility of being allocated also in Europe. This investigation does not include post-transplant follow-up.

Clinical data include age, etiology of brain death, body mass index (BMI), risk factors (hypertension, diabetes mellitus, smoking habit and known previous coronary artery disease) and description of hemodynamics (systolic and diastolic blood pressure, heart rate and the use of norepinephrine or dopamine) in the phase preceding organ removal.

Donor management

All potential donors were managed according to standardized organizational practice guidelines [6–8], as we previously described [9]. These include administration of inotropic agent to maintain mean arterial pressure > 70 mmHg. The hemodynamic management comprises: the use of intravenous fluids to maintain central venous pressure of 6–10 and urine output 1.2 ml/kg/h; correct anemia to maintain hemoglobin ≥ 10 g/dl; electrolyte management; ventilatory management to reach partial pressure of oxygen ≥ 90 mmHg [10].

The use of vasoactive drugs and values of systolic and diastolic blood pressure (SBP and DBP, respectively) and heart rate (HR) were recorded.

Statistical analysis

Data have been processed with IBM-SPSS 20 statistical package (SPSS Inc, Chicago, IL). A two-tailed p value < 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean \pm standard deviation (SD). For continuous variables, between-groups comparisons have been performed with Student's t test or ANOVA (followed by Bonferroni post-tests if overall p was significant) or by means of Kruskal–Wallis H test. Categorical variables have been compared with Chi-square.

Results

Between 2001 and 2016, there were 1286 brain-death potential heart donors (Table 1). The age of potential donors significantly increased ($p=0.02$) as well as the proportion of

patients aged > 55 years. The incidence of hypertension, diabetes mellitus and previously known coronary artery disease significantly increased between the two periods (Table 1).

When comparing the two periods (2001–2008 vs 2009–2016) (Table 1), the relative proportion of post-anoxic brain death progressively increased while that of traumatic brain injury decreased ($p=0.0007$). A significant increase in the use of norepinephrine was detectable, while dopamine was less frequently used in period 2 compared to period 1 (Table 1).

Table 2 shows the number of transplanted hearts according to the causes of brain death. Traumatic brain injury is the main cause for transplanted hearts accounting for about one-third of all transplanted hearts.

As depicted in Table 3, when comparing the two study periods, the number of transplanted hearts did not significantly change, with no differences in the age of donors or in the causes of brain death. No difference was detectable in the incidence of hypertension, diabetes mellitus or smoking habit. When comparing the two periods, norepinephrine was more frequently used in period 2 (Table 3), while dopamine was less frequently used in period 2 in comparison with period 1 in patients eligible for heart transplantation.

Discussion

The main findings of the present investigation, performed in 1286 consecutive potential heart donors after brain death are as follows: (a) during the study period, the age of donors significantly increased, as well as the incidence of risk factors (hypertension, diabetes and coronary artery disease); (b) the incidence of different causes of brain deaths changed due to a reduction in that of traumatic brain injury and an increase in post-anoxic encephalopathy; (c) the number of transplanted hearts did not change during the study period.

Previous papers examined the epidemiological characteristics of brain death in different countries. In Southern Alberta, from 2003 to 2014 [1], a relative decline in the proportion of donors with traumatic brain injury and an increase in those with anoxic brain injury were observed in a cohort of 226 brain-death donors. A decrease in the proportion of organ donors with traumatic brain injury is also reported by investigators in the United States [2, 3] and by studies in Belgium [4, 5]. Though, different from previous papers, we specifically investigated the distribution of causes of brain death in potential heart donors (that is aged < 60 years), a significant reduction in the proportion of donors with traumatic brain injury is also observed in our cohort (from 31.5 to 24%). An increase in the percentage of brain dead patients with post-anoxic encephalopathy is also detectable in our series, in agreement with previous investigation in Canada [1] and Israel [11]. In our 15-year study period,

Table 1 Demographics of potential donors

	2001–2008	2009–2016	<i>p</i>
Number	619	667	
Age (mean ± SD)	43.8 ± 12	48.1 ± 9	0.0001*
Aged > 55 (<i>n</i>)	122 (19.7%)	156 (23.4%)	0.001#
Risk factors	524	597	
Body Mass Index	24.9 ± 5	25.3 ± 3	0.079*
Hypertension (<i>n</i> %)	134 (21.6%)	199 (29.8%)	0.004#
Diabetes mellitus (<i>n</i> %)	29 (4.7%)	66 (9.9%)	0.001#
Smoking habit (<i>n</i> %)	169 (27.3%)	217 (32.5%)	0.149#
Coronary artery disease (<i>n</i> %)	41 (6.6%)	75 (11.2%)	0.009#
Causes (<i>n</i> , %)			
Cerebral hemorrhage	319 (51.5%)	351 (52.6%)	0.0007 #
Traumatic brain injury	195 (31.5%)	160 (24%)	
Anoxic brain injury	40 (6.5%)	72 (10.8%)	
Ischemic stroke	39 (6.3%)	36 (5.4%)	
Other	26 (4.2%)	48 (7.2%)	
Vasoactive drugs			
Noradrenalina (<i>n</i> , %)	253 (40.8%)	368 (55.2%)	0.0001#
Dopamine (<i>n</i> , %)	220 (35.5%)	119 (17.8%)	0.0001#
SBP (median, IQR)	120 (102–135.25)	120 (110–138)	0.535KW
DBP (median, IQR)	70 (56–80)	70 (60–80)	0.534KW
HR (median, IQR)	90 (76.25–105)	92.5 (80–108)	0.107KW

SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, SD standard deviation, IQR interquartile range, KW Kruskal–Wallis

*Student's *t* test

#Chi-square test

Table 2 Heart procurement according to causes of brain death

	Cerebral hemorrhage	Traumatic brain injury	Anoxic brain injury	Ischemic stroke	Other
Number	670	355	112	75	74
Age (mean ± SD)	44.5 ± 11	45.8 ± 11	47.8 ± 10	44.5 ± 10	45.2 ± 14
Time interval from brain injury till brain death diagnosis (median, range; mean ± SD, hours)	46 (2–4440) 115 ± 263	45 (2–1488) 90 ± 146	67 (6–1221) 137 ± 200	86 (6–2235) 175 ± 350	50 (4–1056) 126 ± 182
Transplanted hearts (<i>n</i> %)	99 (14.7%)	113 (31.8%)	8 (7.1%)	6 (8%)	10 (13.5%)

the demographic characteristics of brain death donors (aged > 60) also changed since we documented an increase in mean age and in the proportion of patients aged > 55. This is in keeping with Cohen et al. [11] who report a significant increase in mean age of brain dead donors in Israel from 2004 to 2014. Similar to previous papers [1, 11], we observe that donors became not only older, but also more complex due to the significant increase in the incidence of hypertension, diabetes and previously known coronary artery disease. It can be hypothesized that both donor management and procurement could be more challenging in the following years.

In the investigation by Cohen and al. [11], an increased age of donors resulted in a marked decreased in heart

utilization. Different from Cohen et al. [11], in our investigation, which is the first survey of its kind in Italy, changes in demographic characteristics in brain dead potential heart donors did not affect the numbers of transplanted hearts throughout the study period. In our words, trauma is declining as a fatal disease in Tuscany as worldwide, but that doesn't appear to have an impact on donor hearts procurement in our region. This finding strongly suggests that the heart transplantation system did manage to face the changes in demographic characteristics of brain death by maintaining the same number of transplanted hearts. Factors contributing to this finding have not specifically investigated. However, it can be hypothesized that criteria for organ acceptance did

Table 3 Demographics of transplanted hearts

	2001–2008	2009–2016	<i>p</i>
Transplanted hearts (<i>n</i> , %)	116 (37.2%)	120 (35.9%)	0.92#
Age (mean ± SD)	36.4 ± 12	38 ± 12	0.30*
Aged > 55 (<i>n</i> , %)	7 (1.1%)	13 (1.9%)	0.18#
BMI (mean ± SD)	24.3 ± 3.7	24.8 ± 3.4	0.281*
Hypertension	13 (2.1%)	20 (2.99%)	0.226#
Diabetes	1 (0.2%)	1 (0.15%)	0.980#
Smoke	30 (4.8%)	38 (5.7%)	0.324#
Causes (<i>n</i> , %)			
Cerebral hemorrhage	55 (47.4%)	44 (36.6%)	0.27#
Traumatic brain injury	53 (45.7%)	60 (50%)	
Anoxic brain injury	3 (2.6%)	5 (4.2%)	
Ischemic stroke	1 (0.9%)	5 (4.2%)	
Other	4 (3.4%)	6 (5%)	
Vasoactive drugs			
Noradrenalina (<i>n</i> , %)	64 (10.3%)	94 (14.1%)	0.0001#
Dopamine (<i>n</i> , %)	57 (9.2%)	60 (8.9%)	0.0001#
SBP (median, IQR)	120 (110–140)	125.5 (115.5–140)	0.949KW
DBP (median, IQR)	70 (60–80)	70 (80–106.5)	0.782KW
HR (median, IQR)	90 (82–104)	90.5(80–106.5)	0.839KW

SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, SD standard deviation, IQR interquartile range, KW Kruskal–Wallis

*Student's *t* test

#Chi square test

not significantly change over the study period, since in our cohort, the percentage of donors aged > 55 is not different between the two periods, and the demographic characteristics of heart donors did not change (in terms of age, risk factors and causes of brain death). The possibility that an improved donor management may have made a contribution to the unchanged number of transplanted heart cannot be ruled out, since a different use of vasoactive drugs was observed between the two periods. However, the shift to norepinephrine observed in the period 2009–2016 may be evidence-based since in 2010 in a multicenter randomized trial, the use of dopamine was associated with a greater number of adverse events in respect to norepinephrine in the treatment of shock [12].

Limitation of the study

This is an observational investigation. However, it includes a large number of potential donors (aged < 60), enrolled over a 15-year period. It, therefore, allows insights in the

demographic characteristics of potential donors in our Region and in the organ transplantation system.

Conclusion

These are the two main findings of our investigation performed in a cohort of 1286 potential heart donor (aged ≤ 60) over a 15-year period. Firstly, throughout the study period (15 years), potential heart donors (aged ≤ 60) show epidemiological changes, that is increasing age and a change in BD causes, (mainly a reduction in the incidence of traumatic brain injury). These findings strongly suggest that the organ transplantation system should monitor potential donor epidemiologic variations to “adapt” the system itself. Secondly, when examining heart procurement, no change is detectable in heart procurement despite an increasing donor age. Reasons underlying this phenomenon can only be hypothesized. A change in potential donor management (as indicated by a different use of vasoactive drugs between the two periods) might account for this finding. Conversely, expanding donor criteria (“marginal donors”) can be ruled out since no difference in age is observed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study was approved by the Institutional Review Board of Regional Authority for Transplantation and it is in accordance with Helsinki Declaration of 1975.

Informed consent None.

References

- Kramer AH, Doing CJ, Baht R (2017) Time trends in organ donation after neurologic determination of brain death: a cohort study. *CMAJ Open* 5(1):19–27. <https://doi.org/10.9778/cmajo.20160093>
- Callahan DS, Kim D, Bricker S, Neville A, Putnam B, Smith J, Bongard F, Plurad D (2014) Trends in organ donor management: 2002 to 2012. *J Am Coll Surg* 219:752–756
- Saidi RF, Markmann JF, Jabbour N, Jabbour N, Li Y, Shah SA, Cosimi AB, Bozorgzadeh A (2012) The faltering solid organ donor pool in the United States (2001–2010). *World J Surg* 36:2909–2913
- Van Gelder F, Delbouille MH, Vandervennet M, Van Beeumen G, Van Deynse D, Angenon E, Amerijkx B, Donckier V (2009) An 11-year overview of the Belgian donor and transplant statistics based on a consecutive yearly data follow-up and comparing two periods: 1997–2005 versus 2006–2007. *Transplant Proc* 41:569
- Desschans B, Evrard P (2014) Organ donation and transplantation statistics in Belgium for 2012 and 2013. *Transplant Proc* 46:3124–3126

6. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB (2004) Care of the potential organ donor. *N Engl J Med* 351:2730–2739
7. Frontera JA, Kalb T (2010) How I manage the adult potential organ donor: donation after neurological death. *Neurocrit Care* 12:103–110
8. Zaroff JG, Rosengard BR, Armstrong WF, Babcock WD, D'Alessandro A, Dec GW, Edwards NM, Higgins RS, Jeevanandam V, Kauffman M, Kirklin JK, Large SR, Marelli D, Peterson TS, Ring WS, Robbins RC, Russell SD, Taylor DO, Van Bakel A, Wallwork J, Young JB (2002) Consensus Conference Report. Maximizing use of organs recovered from the cadaver donor: cardiac recommendations. Crystal City, Virginia, USA: ASTS-AST; March 28–29, 2001. *Circulation* 106:836–884
9. Lazzeri C, Guetti C, Migliaccio ML, Ciapetti M, Peris A (2017) The utility of serial echocardiograms for organ procurement in brain death. *Clin Transplant*. <https://doi.org/10.1111/ctr.13094>
10. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB (2002) Care of the potential organ donor. *N Engl J Med* 351:2730–2739
11. Cohen J, Bistriz Y, Ashkenazi T (2015) Deceased organ donor characteristics and organ utilization in israel, 2004–2013. *IMAJ* 17:365–369
12. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators (2010) Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 362(9):779–789