Use of imaging studies for determination of brain death in South Australian intensive care units

Brett G Sampson, Luke D Datson and Shailesh Bihari

ABSTRACT

Objectives: To describe the use of imaging studies (four-vessel angiography or radionuclide scan) for brain death determination in South Australian intensive care units, and to determine the rates of adherence with *The ANZICS statement on death and organ donation* of the Australian and New Zealand Intensive Care Society (ANZICS).

Design, patients and setting: Retrospective case-note review of 190 South Australian adult patients (≥ 18 years) who were brain dead and were organ donors (actual and intended), from 1 January 2008 to 31 December 2014.

Main outcome measures: We compared brain death determination by clinical examination and by imaging, and identified, using logistic regression, the independent predictors of brain death determination by imaging (and for imaging without a documented indication).

Results: Brain death determination by imaging occurred for 79 patients who were brain-dead donors (41.6%), with a documented indication in only 38 patients (48.1%), of whom 35 had an indication which adhered to ANZICS recommendations. The group who had brain death determined by imaging were younger ($P < 0.001$), with a higher proportion of hypoxic brain injury ($P = 0.01$) and therapeutic hypothermia ($P = 0.02$). Independent predictors of brain death determination by imaging were female sex ($\beta = 3.101$, $P = 0.03$), age ($\beta = 0.964$, $P = 0.01$), brain death determination between 5 pm and 8 am ($\beta = 0.332$, $P = 0.04$), cause of death ($\beta = 1.833$, $P = 0.04$), therapeutic hypothermia ($\beta = 0.162$, $P = 0.04$) and terminal serum sodium level ≥ 150 mmol/L ($\beta = 0.131$, $P = 0.005$); Nagelkerke $R^2 = 0.669$. Hypoxia was the only independent predictor of imaging without a documented ANZICS indication ($\beta = 0.071$, $P = 0.032$; Nagelkerke $R^2 = 0.581$).

Conclusions: Therapeutic hypothermia, terminal serum sodium level ≥ 150 mmol/L and cause of death were independent predictors of brain death determination by imaging study. Documentation of imaging indication was poor, particularly after hypoxic brain injury. This may reflect emerging indications for imaging, poor adherence to ANZICS recommendations, or simple omissions.

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The Australian and New Zealand Intensive Care Society (ANZICS), in The ANZICS statement on death and organ donation, makes recommendations for brain death determination by imaging (four-vessel angiography or radionuclide scan). ANZICS recommends that imaging should be reserved for patients for whom pre-conditions for clinical examination cannot be satisfied, or when the clinical examination cannot be completed due to physiological instability or uncertainty of examination findings.[1] However, the way imaging studies are used for the determination of brain death in Australian intensive care units and how well the ANZICS recommendations are adhered to are currently unknown.

Determination of brain death by clinical examination can occur any time of the day, with minimal disruption to patient care, families and the donation process. In contrast, imaging studies are costly, resource-intensive interventions that have the potential to delay the donation process. Imaging studies also have risks associated with transporting a patient undergoing mechanical ventilation out of the ICU and, in the case of four-vessel angiography, additional risks of major vessel injury, bleeding and exposure to intravenous contrast agents.

We aimed to describe the use of imaging studies for the determination of brain death in South Australian ICUs, and to determine how often imaging for brain death determination occurred outside the ANZICS recommendations.

Methods

Patients and setting

We studied adult brain-dead organ donors (aged ≥ 18 years) from the four tertiary referral hospitals in South Australia from 1 January 2008 to 31 December 2014. The patients included actual donors and intended donors (those who were consented for donation but did not proceed). Ethics approval was granted by the Flinders Medical Centre Ethics Committee (approval 190.14HREC/14/SAC/193).

Data collection

A retrospective review of the brain death determination form (BDDF), patient record, donor record, ICU chart and electronic results of investigations was undertaken by one investigator (L D). Data were collected on paper case report forms and entered into an Excel spreadsheet (Microsoft).

Brain death determination form

All included patients had a BDDF completed before proceeding to donation after brain death. The form, adapted from the ANZICS template, included two separate checklists: one for pre-conditions and one for the components of the clinical examination.[1] It was completed by two suitably qualified doctors before brain death was determined.

When pre-conditions were not satisfied or the examination could not be completed, a separate section was completed for determination of brain death by imaging study. However, the BDDF did not have provision for documenting the indication for imaging.

Brain death determination by clinical examination

When brain death was determined by clinical examination, we reviewed the BDDF and patient record for documented evidence of adherence to all ANZICS requirements relating to observation period, pre-conditions and clinical testing.[1] The observation period required at least 4 hours of unresponsive coma (a Glasgow Coma Scale score of 3), with pupils non-reactive to light, an absent cough or tracheal reflex and no spontaneous breathing efforts. Following hypoxic brain injury from cardiopulmonary arrest, clinical examination was delayed for at least 24 hours after the resuscitation or 24 hours after rewarming to 35°C (when therapeutic hypothermia was instituted).[1]

Brain death determination by imaging

All hospitals had 24-hour access to four-vessel cerebral angiography and/or radionuclide perfusion scanner for the entire study period. One hospital (Hospital 1) had access to a bedside radionuclide scanner suitable for testing for brain death within the ICU. The BDDFs and patient records were examined for a documented indication for imaging, defined as failure to satisfy any pre-condition(s) or clinical examination requirement(s) on the BDDF, or the existence of a separate entry in the patient record outlining the indication for imaging. When it was not possible to determine an indication from the BDDF or patient record, "no indication documented" was recorded. Indications for imaging were classified as shown in Table 1.

Clinical examination versus imaging

We analysed the following variables for baseline comparisons between brain death determination by clinical examination and imaging, and for independent predictors for imaging: age, sex, hospital, year of death, Acute Physiology and Chronic Health Evaluation (APACHE) III score, cause of brain death (cerebrovascular accident [CVA], trauma, hypoxia or other), time to brain death determination from admission to hospital, after-hours determination of brain death (between 5 pm and 8 am), documented ANZICS indication for imaging study, neurosurgical intervention (any neurosurgical procedure, extraventricular drain, intracranial pressure monitor, decompressive craniectomy or haematoma evacuation), medical treatments received (therapeutic hypothermia, desmopressin, inotrope or vasopressor [noradrenaline, adrenaline, dobutamine and milrinone] and vasodilator [glyceryl trinitrate and sodium nitroprusside]), sedation within 24 hours of brain death determination, temperature ≥ 35°C at time of brain death determination, last recorded serum sodium level before brain death determination ≥ 150 mmol/L (arterial blood gas or laboratory value), and the last available partial pressure of oxygen:fraction of inspired oxygen ratio.

Table 1. Classification of indications for brain death determination by imaging study

1.* Pre-conditions not met, defined as not meeting any of the following:
   - normothermia, defined as ≥ 35°C
   - normotension, defined as mean arterial pressure 60 mmHg
   - exclusion of the effects of sedative drugs
   - absence of severe metabolic or endocrine disturbances
   - intact neuromuscular function
   - ability to examine the brainstem reflexes
   - ability to perform the apnoea test.

2.* Inability to complete one or both clinical brain death examinations including cervical spine injury, inability to examine at least one eye and one ear, or the inability to complete apnoea test.

3.* Uncertainty of motor response to pain, defined as inability to distinguish between a spinal reflex and a true motor response to noxious stimuli.

4. Intensivist preference for imaging study; a documented preference for imaging in the absence of any of the above indications.

5. No indication documented.

ANZICS = Australian and New Zealand Intensive Care Society.
* Adapted from *The ANZICS statement on death and organ donation.*[1]

Statistical analysis

We performed statistical analyses using PASW Statistics, version 22.0 (IBM). Data were tested for normality with the Shapiro–Wilk test and normalised by log transformation where necessary. Data are reported as means with standard deviations (SDs), or medians with interquartile ranges (IQRs), as appropriate for the distribution of each variable. For comparisons, we analysed normally distributed data with the Student *t* test, non-normally distributed data with the Mann–Whitney *U* test and categorical data with the Pearson χ^2 test or the Fisher exact test, as appropriate. Logistic regression was used to identify independent predictors for the mode of brain death determination (clinical examination versus imaging study), and to identify independent predictors of an imaging study being performed without a documented ANZICS indication. $P < 0.05$ was considered significant.

Table 2. Donor characteristic comparisons between brain death determination by clinical examination and by imaging study

Variable	Clinical examination (*n* = 111)	Imaging* (*n* = 79)	*P*†
Median age, years (IQR)	57 (44.5–69.5)	45 (31.5–58.5)	< 0.001
Men, *n* (%)	64 (57.7%)	43 (54.4%)	0.66
Median APACHE III score (IQR)	100 (81–119)	107 (88.5–126.5)	0.06
Cause of death, *n* (%)			
CVA	74 (66.6%)	32 (40.5%)	0.002
Trauma	18 (16.2%)	18 (22.7%)	0.35
Hypoxia	17 (15.3%)	25 (31.6%)	0.01
Other	2 (1.8%)	4 (5.0%)	0.40
Median time to death, from admission to hospital, days (IQR)	1.49 (0.59–2.40)	1.34 (0.28–2.40)	0.63
Determination of death between 5 pm and 8 am, *n* (%)	28 (25.2%)	30 (38.0%)	0.06
Hospital, *n* (%)			
Hospital 1	58 (52.3%)	43 (54.4%)	0.77
Hospital 2	39 (35.1%)	19 (24.1%)	0.11
Hospital 3	10 (9.0%)	11 (13.9%)	0.35
Hospital 4	4 (3.6%)	6 (7.6%)	0.32
Neurosurgical intervention, *n* (%)			
Any neurosurgical procedure	21 (18.9%)	19 (24.0%)	0.39
ICP monitoring	3 (2.7%)	4 (5.0%)	0.40
EVD insertion	7 (6.3%)	8 (10.1%)	0.34
Decompressive craniectomy	11 (9.9%)	9 (11.4%)	0.74
Haematoma evacuation	4 (3.6%)	2 (2.5%)	0.68
Medical treatments received, *n* (%)			
Therapeutic hypothermia	4 (3.6%)	10 (12.6%)	0.02
Desmopressin	55 (49.5%)	32 (40.5%)	0.22
Inotrope or vasopressor	96 (86.4%)	63 (79.7%)	0.22
Vasodilator	7 (6.3%)	3 (3.8%)	0.45
Sedation within previous 24 h, *n* (%)	1 (0.9%)	2 (2.5%)	0.37
Serum sodium‡ 150 mmol/L, *n* (%)	20 (18.1%)	19 (24.1%)	0.36
Temperature 35°C at time of brain death determination, *n* (%)	111 (100%)	79 (100%)	1.00
Median P:F ratio‡ (IQR)	347.33 (252.83–441.83)	326.67 (242.17–411.17)	0.08

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. CVA = cerebrovascular accident (including ischaemic and haemorrhagic injuries). ICP = intracranial pressure (excluding EVD). EVD = extraventricular drain. P:F = partial pressure of oxygen:fraction of inspired oxygen. * Imaging by four-vessel angiography or radionuclide scan. † Non-normally distributed continuous data analysed with Mann–Whitney *U* test; categorical data analysed with Pearson χ^2 test. ‡ Last available value before brain death determination.

Results

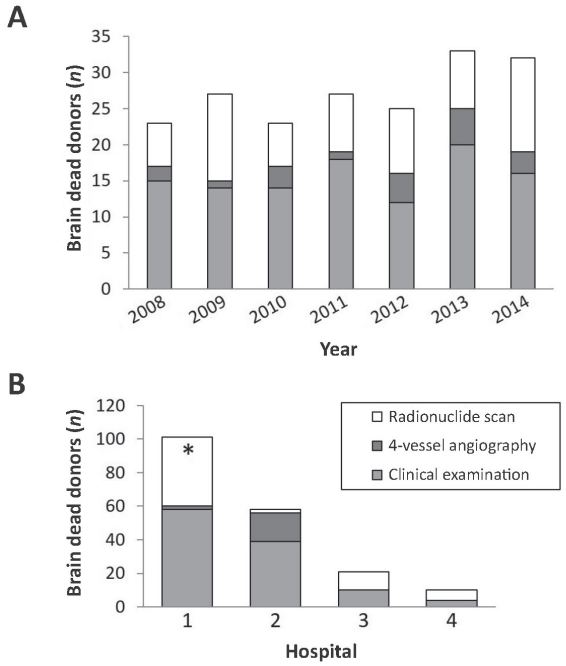
Patients

There were 190 brain-dead donors (actual and intended donors) in South Australia for the study period, all of whom we included in our study. There were 111 donors (58%) determined to be brain dead by clinical examination, all of whom had documented adherence to ANZICS observation periods, pre-conditions and clinical tests. Of the 79 imaging studies performed, 62 (78%) were by radionuclide scan, of which 41 (66%) were done with a bedside radionuclide scanner (all at Hospital 1).

Clinical examination versus imaging

The group of donors who were determined brain dead by imaging were younger, with a higher proportion of hypoxia as the cause of death, and a higher proportion had undergone therapeutic hypothermia. Brain death determination by clinical examination occurred more often when CVA was the cause of death (Table 2). All patients were normothermic (≥ 35°C) at the time of brain death determination, with only one patient determined brain dead (by imaging study) within 24 hours of rewarming after therapeutic hypothermia. Other patient characteristics

Figure 1. Method of brain death determination in South Australia, (A) by year and (B) by hospital



* Bedside radionuclide scan.

and comparisons between brain death determination by clinical examination and imaging study are shown in Table 2. The method of brain death determination, by year and by hospital, are shown in Figure 1.

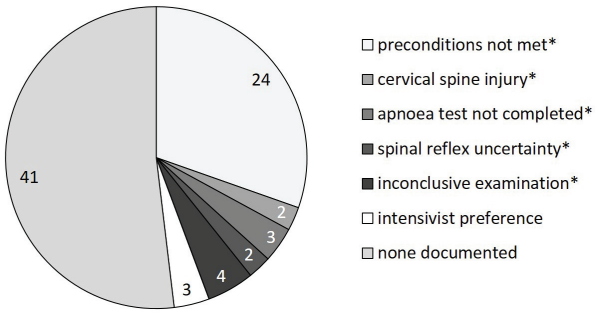
Predictors of brain death determination by imaging study

Independent predictors of brain death determination by imaging were: female sex (β = 3.101, P = 0.03), age (β = 0.964, P = 0.01), brain death determination between 5 pm and 8 am (β = 0.332, P = 0.04), cause of death (β = 1.833, P = 0.04), therapeutic hypothermia (β = 0.162, P = 0.04) and terminal serum sodium level ≥ 150 mmol/L (β = 0.131, P = 0.005); Nagelkerke R^2 = 0.669.

ANZICS indication for brain death determination by imaging study

An indication for brain death determination was documented in 38 patients (48%) determined brain dead by imaging; 35 were in accordance with ANZICS recommendations (44% of all donors) and the remaining three documented indications were for intensivist preference (Figure 2). No donor had more than one documented indication. Of the 10 donors in the imaging group who underwent therapeutic hypothermia, one had a documented ANZICS indication, one was for intensivist preference, and the remaining eight had no indication documented. Among donors without a documented ANZICS indication for imaging, there was a higher proportion with hypoxia as the cause of death and a higher proportion underwent therapeutic hypothermia (Table 3). Logistic regression (Nagelkerke R^2 = 0.581) showed that documentation of an ANZICS indication improved throughout the study period (β = 2.249, P = 0.004), with increasing time to brain death (β = 1.722, P = 0.02) and with inotropic support (β = 23.376, P = 0.02). Hypoxic brain injury (β = 0.071, P = 0.03) was the only independent predictor of lack of a documented ANZICS indication.

Figure 2. Documented indications for performing an imaging study (four-vessel angiography or radionuclide scan) for brain death determination (n = 79)



ANZICS = Australian and New Zealand Intensive Care Society.
* Indications consistent with *The ANZICS statement on death and organ donation.*[1]

Discussion

Main findings

This study provides the first description of Australian brain death determination practices in the ICU. Independent predictors for brain death determination by imaging were female sex, age, after-hours brain death determination, cause of death, therapeutic hypothermia and terminal serum sodium level ≥ 150 mmol/L. A documented ANZICS indication for brain death determination by imaging was absent for more than 50% of imaging studies. The absence of indication occurred more often in patients with hypoxic brain injury and those having undergone therapeutic hypothermia. However, only hypoxic brain injury was an independent predictor of imaging without a documented ANZICS indication.

International comparisons

While ANZICS recommends either four-vessel angiography or radionuclide scan for confirming absent intracranial blood flow, additional ancillary tests are recommended

Table 3. Determination of brain death by imaging study, comparing donors with and without a documented ANZICS indication

Variable	ANZICS indication*		$P^{\dagger}$
	Yes (n = 35)	No (n = 44)	
Median age, years (IQR)	30.5 (45–56.5)	30 (41.5–57.75)	0.29
Men, *n* (%)	22 (62.9%)	21 (47.7%)	0.13
Median APACHE III score (IQR)	114 (89.5–123.0)	101.5 (81.8–123.5)	0.10
Cause of death, *n* (%)			
CVA	13 (37.1%)	19 (43.2%)	0.65
Trauma	13 (37.1%)	5 (11.4%)	0.01
Hypoxia	6 (17.1%)	19 (43.2%)	0.02
Other	3 (8.5%)	1 (2.3%)	0.32
Median time to death, from admission to hospital, days (IQR)	1.08 (0.87–2.30)	1.57 (0.86–3.30)	0.13
Determination of death between 5 pm and 8 am, *n* (%)	13 (37.1%)	17 (38.6%)	1.0
Neurosurgical intervention, *n* (%)			
Any neurosurgical procedure	9 (25.7%)	10 (22.7%)	0.80
ICP monitoring	1 (2.9%)	3 (6.8%)	0.63
EVD insertion	1 (2.9%)	7 (15.9%)	0.07
Decompressive craniectomy	4 (11.4%)	5 (11.4%)	1.00
Haematoma evacuation	2 (5.7%)	0	0.19
Medical treatments received, *n* (%)			
Therapeutic hypothermia	1 (2.9%)	9 (20.5%)	0.03
Desmopressin	13 (37.1%)	19 (43.2%)	0.65
Inotrope or vasopressor	29 (82.9%)	34 (77.3%)	0.59
Vasodilator	1 (2.9%)	2 (4.5%)	1.00
Sedation within previous 24 h, *n* (%)	2 (5.7%)	0	0.19
Serum sodium‡ ≥ 150 mmol/L, *n* (%)	10 (28.6%)	9 (20.5%)	0.44
Temperature ≥ 35°C at time of brain death determination, *n* (%)	35 (100%)	44 (100%)	1.00
Median P:F ratio‡ (IQR)	327.83 (266.83–385.96)	307.5 (216–400)	0.64

ANZICS = Australian and New Zealand Intensive Care Society. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. CVA = cerebrovascular accident (including ischaemic and haemorrhagic injuries). ICP = intracranial pressure (excluding EVD). EVD = extraventricular drain. P:F = partial pressure of oxygen:fraction of inspired oxygen. * Indications consistent with *The ANZICS statement on death and organ donation*.[1] † Non-normally distributed continuous data analysed with Mann–Whitney *U* test; categorical data analysed with Pearson χ^2 test. ‡ Last available value before brain death determination.

internationally, with wide variability between countries.[1-9] These tests include electroencephalography, transcranial Doppler study and computed tomography (CT) cerebral angiography. In its statement, ANZICS does not currently recommend CT angiography and considers transcranial Doppler to be a screening test only.[1] The proportion of donors undergoing brain death determination by radionuclide scan in one United States study was 35.4%, which is comparable with our results. An additional 12.8% of donors underwent CT cerebral angiography, but it was not reported how many had both tests performed.[2] A large Spanish study found only 0.5% and 8% of brain-dead donors had four-vessel angiography and radionuclide scan, respectively, but 2.5% underwent CT angiography and 37%, transcranial Doppler study.[3] Again, it was not possible to determine how many donors in the Spanish study had more than one of these ancillary tests of intracranial blood flow. It is possible that our findings may have been different had additional ancillary tests been recommended by ANZICS.

The 100% adherence to ANZICS recommendations for clinical brain death determination in our study compares favourably with the poor adherence found in the US.[2,10,11] This is likely explained by the standardisation of the BDDF in our jurisdiction.

Documentation of imaging indication

The poor documentation of the indication for imaging is consistent with US practice.[2] There are three possible explanations for this in our study. First, the lack of provision on the BDDF for entering the indication may account for

an existing ANZICS indication not being documented (ie, a simple omission). Second, the intensivist might have made a conscious decision to perform an imaging study outside accepted practice. Last, it is possible that additional valid indications for imaging are not currently included in the ANZICS statement. Our findings cannot differentiate between these three explanations, but the latter two might explain why hypoxic brain injury was a predictor for imaging without a documented ANZICS indication.

Hypoxic brain injury

Early bedside prognostication after hypoxic brain injury from cardiac arrest is challenging, especially with the uncertain effects on clinical examination of therapeutic hypothermia and deep sedation.[12-16] This may explain our findings of cause of death and therapeutic hypothermia being independent predictors for imaging, especially in the absence of a documented indication. That is, the uncertainty about prognosis after hypoxic brain injury may have resulted in increased intensivist preference to order an imaging study, particularly after therapeutic hypothermia. Further, the uncertain effects of therapeutic hypothermia have resulted in ANZICS recommending that clinical testing for brain death be delayed for 24 hours after rewarming.[1] In addition, initial neuroimaging in hypoxic brain injury is rarely indicated and, when performed, is often normal or inconclusive, which might further influence a decision to perform confirmatory brain death imaging. In contrast, the often catastrophic appearance of initial neuroimaging scans after a CVA might explain why brain death determination by clinical examination was significantly higher in this group.

Recent published case reports of "reversible" brain death may have also influenced the ordering of imaging studies for brain death determination.[17,18] Perhaps the most important case was a 55-year-old man determined brain dead by clinical examination after hypoxic arrest and therapeutic hypothermia, in whom brainstem reflexes returned after consent for organ donation had been obtained.[18] An accompanying editorial suggested residual sedation, brainstem neural hibernation or inadvertent pancuronium administration as possible explanations for the reversibility of lost brainstem reflexes. This is unlikely to reassure the intensivist who is erring towards an imaging study to confirm brain death in such patients.[19]

While it is essential that families understand that their loved one has become brain dead, one study found that only 28% of participating family members were able to provide a correct definition of brain death.[20] Initial neuroimaging may help families understand brain death if the images are easily interpretable, such as after a catastrophic intracranial haemorrhage. However, if initial neuroimaging is not performed or does not adequately illustrate the severity of the injury, such as after hypoxia, then a radionuclide scan or four-vessel angiography might be ordered solely to improve family understanding. Ancillary tests might also be necessary when families refute the validity of clinical brain death testing, particularly when they have knowledge of publicised cases of "reversible" brain death.[17,18,21] Family understanding might therefore account for some of the imaging studies performed without indication in our study.

Hypernatraemia

Hypernatraemia from hypertonic saline administration or diabetes insipidus is common in patients who are brain dead. When this occurs, the treating intensivist must decide if the hypernatraemia is severe enough to preclude brain death determination by clinical examination. We found that a serum sodium level ≥ 150 mmol/L was an independent predictor for imaging, but our results should be interpreted with caution. Unfortunately, we were not able to determine when a sodium level ≥ 150 mmol/L was the intensivist's reason for the imaging study. Also, in the absence of a threshold serum sodium value in the ANZICS statement, above which an imaging study should be performed, we arbitrarily chose a value of 150 mmol/L. This threshold was possibly too low, which is suggested by the absence of a significant difference in the number of patients in the clinical examination group with a serum sodium level ≥ 150 mmol/L.

Access to imaging studies

The finding that after-hours brain death determination was an independent predictor for using an imaging study suggests that access to imaging studies for brain death determination improves after hours. This is likely to be a reflection of the higher priority given to other imaging studies and procedures during working hours. Although one hospital had access to a bedside radionuclide scanner within the ICU, this did not appear to have increased the use of imaging to determine brain death in that centre. This is suggested by the absence of a significant difference in imaging rates between Hospital 1 and the other hospitals; and by the hospital not being an independent predictor of imaging.

Limitations and future research

Our study had the usual limitations related to its retrospective study design and small sample size. One such limitation was the inability to include patients in the study who were not determined to be brain dead on brain death testing. In addition, it was not possible to include patients who were determined to be brain dead but for whom their families did not consent to organ donation. A potential selection bias therefore existed, as these two patient groups might have had different baseline characteristics and different rates and indications for imaging. The large proportion

of donors undergoing imaging without a documented indication is an important finding, but it is also a major limitation. Our results would be more meaningful had we identified an indication for every imaging study performed. We therefore believe that a prospective study investigating the reasons intensivists order imaging studies for brain death determination is now warranted. Identifying the full spectrum of intensivists' reasons for ordering imaging studies will inform education strategies for improving guideline adherence and limit variability in practice. It will also provide the basis for future research into the validity of emerging indications for brain death determination by imaging. To that end, the results of a Canadian systematic review and meta-analysis of ancillary testing for the diagnosis of brain death are eagerly awaited.[22]

Conclusions

Important independent predictors for brain death determination by imaging study included therapeutic hypothermia, terminal serum sodium level ≥ 150 mmol/L and cause of death. Documentation of imaging indication was poor, particularly after hypoxic brain injury. This may reflect emerging indications for imaging, poor adherence to ANZICS recommendations, or simple omissions.

Competing interests

None declared.

Author details

Brett G Sampson, Intensivist[1] and Donation Medical Specialist[1,2]
Luke D Datson, Donation Specialist Nurse Coordinator[1,2]
Shailesh Bihari, Intensivist[1]

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

Correspondence: brett.sampson@sa.gov.au

References

1 Australian and New Zealand Intensive Care Society. The ANZICS statement on death and organ donation. Edition 3.2. Melbourne: ANZICS, 2013. http://www.anzics.com.au/Pages/DaOD.aspx (accessed Dec 2016).
2 Shappell CN, Frank JI, Husari K, et al. Practice variability in brain death determination: a call to action. *Neurology* 2013; 81: 2009-14.
3 Escudero D, Valentín MO, Escalante JL, et al. Intensive care practices in brain death diagnosis and organ donation. *Anaesthesia* 2015; 70: 1130-9.
4 Shemie SD, Lee D, Sharpe M, et al; Canadian Critical Care Society. Brain blood flow in the neurological determination of death: Canadian expert report. *Can J Neurol Sci* 2008; 35: 140-5.
5 Wijdicks EF, Varelas PN, Gronseth GS, et al; American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2010; 74: 1911-8.
6 Smith M. Brain death: the United Kingdom perspective. *Semin Neurol* 2015; 35: 145-51.
7 Citerio G, Murphy PG. Brain death: the European perspective. *Semin Neurol* 2015; 35: 139-44.
8 Wijdicks EF. Determining brain death. *Continuum (Minneap Minn)* 2015; 21: 1411-24.
9 Wijdicks EF. The clinical determination of brain death: rational and reliable. *Semin Neurol* 2015; 35: 103-4.
10 Greer DM, Wang HH, Robinson JD, et al. Variability of brain death policies in the United States. *JAMA Neurol* 2016; 73: 213-8.
11 Ghoshal S, Greer DM. Why is diagnosing brain death so confusing? *Curr Opin Crit Care* 2015; 21: 107-12.
12 Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. *Crit Care Med* 2014; 42: 1340-7.
13 Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation* 2014; 85: 1779-89.
14 Horn J, Cronberg T, Taccone FS. Prognostication after cardiac arrest. *Curr Opin Crit Care* 2014; 20: 280-6.
15 Taccone F, Cronberg T, Friberg H, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. *Crit Care* 2014; 18: 202.
16 Zingler VC, Krumm B, Bertsch T, et al. Early prediction of neurological outcome after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. *Eur Neurol* 2003; 49: 79-84.
17 Roberts DJ, MacCulloch KA, Versnick EJ, et al. Should ancillary brain blood flow analyses play a larger role in the neurological determination of death? *Can J Anaesth* 2010; 57: 927-35.
18 Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Crit Care Med* 2011; 39: 1538-42.
19 Streat S. "Reversible brain death" — is it true, confounded, or "not proven"? *Crit Care Med* 2011; 39: 1601-3.
20 Siminoff LA, Mercer MB, Arnold R. Families' understanding of brain death. *Prog Transplant* 2003; 13: 218-24.
21 Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. *N Engl J Med* 2014; 370: 891-4.
22 Chassé M, Glen P, Doyle MA, et al. Ancillary testing for diagnosis of brain death: a protocol for a systematic review and meta-analysis. *Syst Rev* 2013; 2: 100. ❑