

## Original Article

## Pupil diameter for confirmation of brain death in adult organ donors in Japan

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**Aim:** The criteria for brain death in Japan include a bilateral pupil diameter of  $\geq 4$  mm. We evaluated the appropriateness of a 4-mm pupil diameter in adult brain-dead donors in Japan.

**Methods:** We retrospectively reviewed the records of 148 consecutive adult brain-dead donors with an average age of 46 years. All records were anonymously registered to the Japanese Ministry of Health, Labour and Welfare (the Japanese Ministry of Health and Welfare before 2001) from the various designated emergency institutes that performed organ donation under brain death from 1999 to 2012 in Japan.

**Results:** All donors had a Glasgow Coma Scale score of 3, absence of all seven brain stem reflexes, an isoelectric electroencephalogram for  $>30$  min, and apnea as tested by the standard method. All of these examinations were repeated approximately 6 h later for confirmation. The pupil diameter (average  $\pm$  standard deviation) was  $6.1 \pm 1.1$  mm at the first assessment and  $6.4 \pm 1.1$  mm approximately 6 h later. The 95% probability distribution as calculated by statistical analysis was 3.93–8.30 mm in the left eye and 3.88–8.28 mm in the right eye in the first assessment, and 4.25–8.58 mm in the left eye and 4.32–8.43 mm in the right eye approximately 6 h later.

**Conclusion:** Despite the various original causes of brain death, we conclude that a pupil diameter of  $\geq 4$  mm is a reasonable criterion for brain death in adults.

**Key words:** Brain death, criteria, Japan, organ donation, pupil diameter

## INTRODUCTION

ACCORDING TO THE official Japanese criteria, brain death is defined as the irreversible loss of all cerebral functions, including those of the brain stem and cerebral hemispheres. The official criteria for brain death were proposed in 1985 by the Brain Death Study Group sponsored by the Japanese Ministry of Health and Welfare (MHW) (Table 1).<sup>1</sup> According to the declaration of brain death for heart-beating organ donors, at least two experienced doctors (usually a neurologist, neurosurgeon, or neurointensivist) who are uninvolved in the transplantation procedure must examine all donors with respect to the following parameters: deep coma (no response to painful stimuli) with a Glasgow Coma Scale score of 3, bilaterally fixed pupils  $>4$  mm in

diameter, totally absent light, corneal, ciliospinal, oculocephalic, vestibular, pharyngeal, and cough reflexes, tested separately on each side, an isoelectric electroencephalogram (EEG) for  $>30$  min (continuous recording), and apnea as confirmed by the standard apnea test (final PaCO<sub>2</sub> of  $>60$  mmHg). All tests are repeated 6 h later for confirmation. After the completion of these tests, the donor is allowed to be prepared for organ donation.

The criteria for brain death in the USA<sup>2,3</sup> require bilaterally fixed pupils of  $>4$  mm in diameter. The pupils must simply be midsize or larger in the Canadian criteria.<sup>4,5</sup> The Australian and New Zealand Intensive Care Society<sup>6</sup> and the German criteria<sup>7</sup> only require the absence of a light reflex. Whether the pupil size is always  $>4$  mm in all cases of brain death remains unknown. Only two observational studies have reported on the pupil size in brain-dead adults<sup>1</sup> and children.<sup>8</sup> In one of these two studies, 26 of 628 (4.1%) left pupils and 28 of 628 (4.5%) right pupils were  $<4$  mm in diameter in brain-dead adults.<sup>1</sup> The other study reported that 7% of left or right pupils were  $<4$  mm in diameter among 162 children suspected to be brain dead but in whom the

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**Table 1.** Criteria of brain death proposed by the Japanese Ministry of Health, Labour and Welfare (Takeuchi's Guidelines)<sup>1</sup>

## Subjects

Patients in a deep coma and apneic as a result of organic brain damage

Patients in whom the cause of brain damage has been definitively diagnosed and in whom the nature of the damage has been judged to be irremediable despite all currently available treatment methods for the disease

## Exclusion criteria

Children <6 years of age

Acute drug poisoning

Hypothermia ( $\leq 32^{\circ}\text{C}$  core body temperature)

Metabolic or endocrine disorder

## Caution before judgment

Exclude the effects of drugs acting on the central nervous system (the drug, dosing method, duration, time after last dose, and effective drug activity period should all be taken into consideration) and muscle relaxants (nerve stimulation should be performed). The systolic blood pressure should be  $\geq 90$  mmHg

Diagnostic criteria (*bold letters denote the three main elements*)

**Deep coma (Glasgow Coma Scale score of 3)**

**Fixed bilateral pupillary diameter of  $\geq 4$  mm**

**Absence of brain stem reflexes**

Light, corneal, cilio-spinal, oculoccephalic, vestibular, pharyngeal, and cough reflexes (test separately on each side)

Flat electroencephalogram (sensitivity of  $\geq 2.5$   $\mu\text{V}/\text{mm}$  is necessary according to the guidelines of the Japanese Society of Electroencephalography and Electromyography)

Absence of spontaneous respiration ( $\text{PaCO}_2 > 60$  mmHg during suspension of mechanical ventilation in the apnea test. Although the method for suspending mechanical ventilation is arbitrary, the administration of 100% oxygen before and during the test is essential)

The apnea test should be the last in the test series

## Observation period

Confirmation of the absence of neurological changes after 6 h (this does not mean that the second examination should be performed exactly 6 h later)

A period of  $> 6$  h should be allowed for patients with secondary brain damage (e.g., after cardiopulmonary resuscitation) and in children  $\geq 6$  years of age

apnea test was not carried out.<sup>8</sup> In the present study, we evaluated the pupil diameter in brain-dead organ donors to determine whether 4 mm is a reasonable criterion for brain death.

## METHODS

**T**HE JAPANESE ORGAN donation process was established by national law in 1997. According to this law, all brain-dead, heart-beating organ donors in Japan must be verified by council members delegated by the Japanese Ministry of Health, Labour and Welfare (MHLW). All records are submitted by the emergency institutes that anonymously donate organs throughout Japan. All of these institutes have been designated as appropriate hospitals based on their ability to carry out brain death diagnosis and organ donation.

In the present study, all examinations were carried out by two experienced doctors (usually a neurologist,

neurosurgeon, or neurointensivist) who belonged to the same institute and were uninvolved in the definitive treatment or transplantation process. Pupil size was carefully measured by each examiner with a 0.5-mm-interval semilunar-shaped ruler under regular brightness before light reflex stimulation. Evaluation of other brain stem reflexes, recording of the EEG for  $> 30$  min, and performance of the apnea test were completed twice by standard methods at a 6-h interval. After completion of all tests, the examiners declared brain death as the time of patient death.

We reviewed all records of both the diagnostic process of brain death and the mediation process of each organ. Because all data were compiled in anonymous records, provided to the Japanese MHLW and Japan Organ Transplant Network by the various designated emergency institutes that carried out organ donation under brain death from 1999 to 2012 in Japan, sufficient consideration was given to the ethical issues in this study.

Statistical analyses were carried out using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). We statistically validated whether the pupil diameters followed a normal distribution. We used the Shapiro–Wilk test to validate the normality of the distribution. The Shapiro–Wilk test can test the null hypothesis that the data are drawn from a normal distribution. When  $P < 0.05$ , the null hypothesis is rejected, indicating that the data are not normally distributed. Some difficulties will arise if the population distribution is unknown; unfortunately, this is the most common scenario in medical research. For large samples, however, we can assume that the distribution is robust and follows a normal distribution despite the fact that the preliminary test reveals no normality.<sup>9</sup>

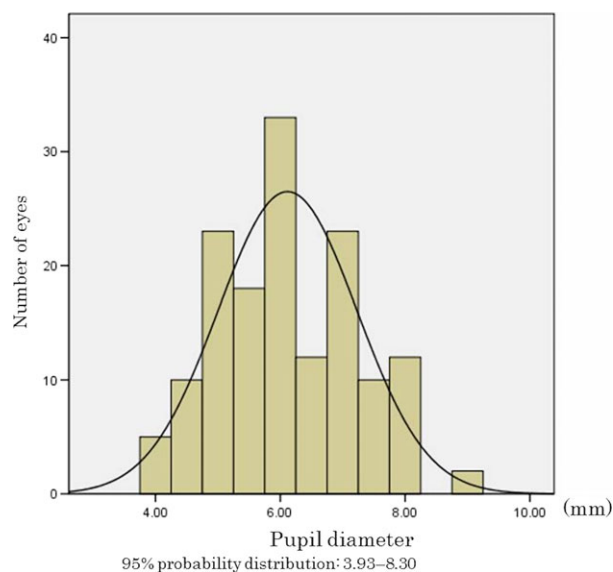
## RESULTS

**I**N TOTAL, 148 consecutive case report forms from 82 male and 66 female donors were examined. Data were collected from 113 donor hospitals throughout Japan. All donors were diagnosed with brain death under the official criteria of the Japanese MHW. All were adult donors ranging in age from 18 to 72 years (average, 46 years). The main causes of brain death were subarachnoid hemorrhage ( $n = 60$ ), head injury ( $n = 23$ ), postcardiac arrest ( $n = 32$ ), brain hemorrhage ( $n = 25$ ), brain infarction ( $n = 6$ ), and brain tumors ( $n = 2$ ). Irreparable brain lesions were detected by computed tomography, and those involving the whole brain, including the brain stem, were considered to be irreversible. The systolic blood pressure was maintained at  $>90$  mmHg with continuous infusion of dopamine, norepinephrine, or vasopressin. The core body temperature was  $\geq 35^{\circ}\text{C}$ . Cases of drug overdose were excluded from this study. The administration of drugs that may influence the neurological evaluation, such as sedatives, opioids, or muscle relaxants, was discontinued for an adequately long period of time before the assessment. Severe endocrine or metabolic disorders were also excluded.

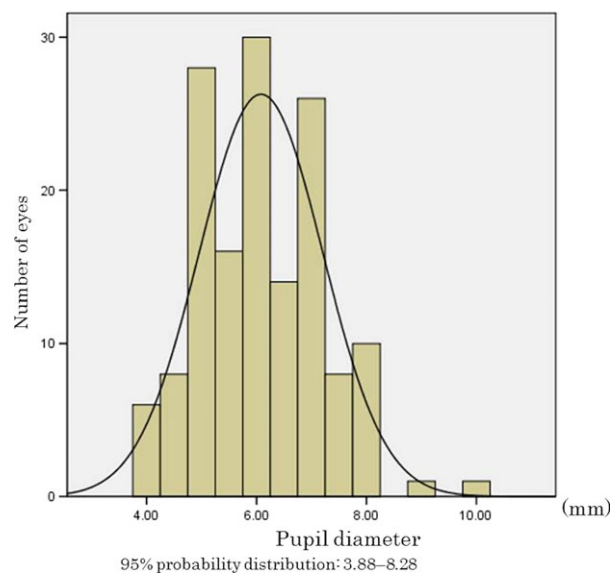
All patients had a Glasgow Coma Scale score of 3 at the first assessment for brain death. Additionally, all patients lacked all seven brain stem reflexes. All pupil diameters were measured in 0.5-mm intervals.

The results of the Shapiro–Wilk test rejected the null hypothesis that the data had been drawn from a normal distribution in all assessments ( $P < 0.05$ ). However, the present study included a large sample; thus, it could be calculated that 95% of values were within 1.96 standard deviations of the mean. The predominant pupil diameter was 6 mm at the first measurement and 7 mm at the second measurement, approximately 6 h later. The average pupil diameter was

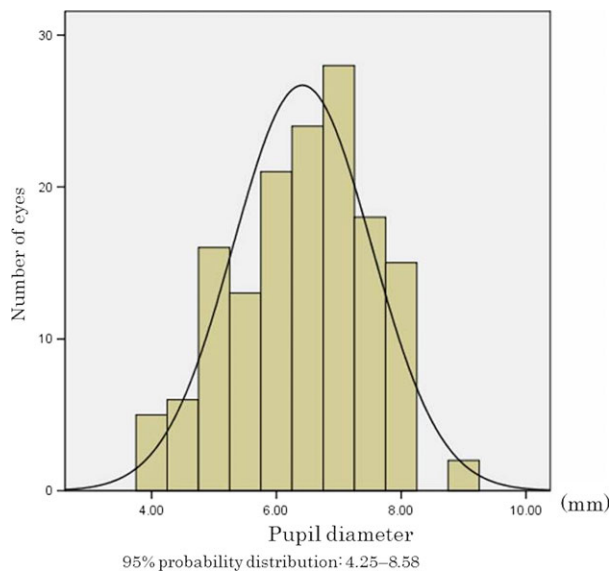
$6.1 \pm 1.1$  mm at the first assessment and  $6.4 \pm 1.1$  mm at the second. The statistically calculated 95% probability distribution was 3.93–8.30 mm in the left eye and 3.88–8.28 mm in the right eye in the first assessment, and 4.25–8.58 mm in the left eye and 4.32–8.43 mm in the right eye 6 h later (Figs. 1–4). The mean diameters were not statistically different among the main causes of brain death (Table 2).



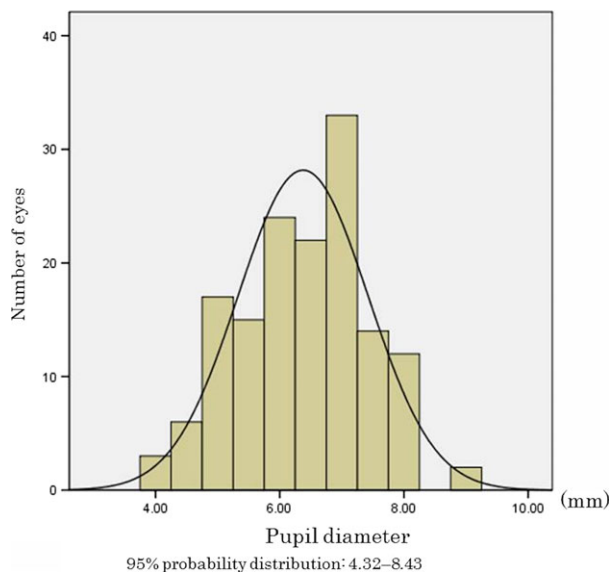
**Fig. 1.** Left pupil diameter in adult brain-dead donors in Japan ( $n = 148$ ), first assessment.



**Fig. 2.** Right pupil diameter in adult brain-dead donors in Japan ( $n = 148$ ), first assessment.



**Fig. 3.** Left pupil diameter in adult brain-dead donors in Japan ( $n = 148$ ). Second assessment carried out 6 h after first assessment.



**Fig. 4.** Right pupil diameter in adult brain-dead donors in Japan ( $n = 148$ ). Second assessment carried out 6 h after first assessment.

Both pupils were fixed and did not react to light stimulation. The other brain stem reflexes, namely the corneal, ciliospinal, oculocephalic, vestibular, pharyngeal, and cough reflexes, were totally absent on both sides. Isoelectric EEG was observed as recorded from 12 monopolar and bipolar

channels with a sensitivity of  $\geq 10.0$  and  $> 2.5$   $\mu\text{V}/\text{mm}$ , respectively. Under adequate preoxygenation and adjustment of the  $\text{PaCO}_2$  to approximately 40 mmHg, absence of spontaneous respiration was observed for several minutes, and mechanical ventilation was interrupted twice to achieve a  $\text{PaCO}_2$  of  $> 60$  mmHg. All patients were considered to be apneic in both assessments. All patients were declared to be brain dead at the end of the second assessment according to the brain death criteria of the Japanese MHW. They began to undergo preparation for organ donation by their own advanced directives or consent from their family.

## DISCUSSION

**I**N JAPAN, THE state of brain death was defined by the Japanese EEG Society in 1974, only 6 years after Harvard Medical School proposed a definition of irreversible coma.<sup>10</sup> A brain death study group was organized under the support of the Japanese MHW in 1983; this group evaluated 718 cases of brain death from 217 hospitals and proposed a definition of brain death in Japan.<sup>1</sup> At that time, a British researcher proposed brain stem death as the definition of brain death.<sup>11</sup> They emphasized the lack of brain stem reflexes and apnea without considering the pupil size. However, the criteria for brain death in Japan defined the whole brain, including both hemispheres, and brain stem death as only one type of brain death.<sup>1</sup> To date, the criteria originally established by the Japanese MHW has not been changed (Table 1). In the process of establishing the Japanese criteria, the MHW studied the pupil diameter. They found that approximately 20% of cases of suspected brain death showed pupil diameters of  $< 4$  mm and that most (60%) were 5–6 mm in diameter.<sup>1</sup> They stated that both pupils must be fixed and lack a light reflex and that the diameter should be  $\geq 4$  mm to qualify as brain death.

According to the worldwide diagnostic criteria for brain death in adults<sup>12</sup> and children,<sup>8</sup> both pupils must be fixed in the midposition and light reflexes must be absent. However, most countries, with the exception of the USA and Japan, have not given pupil size particular consideration. As mentioned above, the Japanese criteria were established on the basis of preliminary research. In the present study, the pupil size in brain death was always  $> 4$  mm throughout the observation period in all adult cases. The predominant diameter was 6–7 mm, and these data were normally distributed. The average pupil diameter was 6.1 mm at the first assessment and 6.4 mm at the second assessment of brain death. The 95% distribution of the pupil diameter in this study ranged from 3.93 to 8.30 mm in the left eye and 3.88–8.28 mm in the right eye in the first assessment, and from 4.25 to 8.58 mm in the left eye and 4.32–8.43 mm in the right eye

**Table 2.** Pupil diameters associated with the various causes of brain death

Assessment/pupil	SAH (n = 60)	Head injury (n = 23)	Post-CPA (n = 32)	Others (n = 33)
First/left	6.36 ± 0.99	6.32 ± 1.07	6.55 ± 1.05	6.25 ± 1.10
First/right	6.43 ± 1.04	6.39 ± 1.14	6.60 ± 1.13	6.23 ± 1.14
Second/left	6.44 ± 0.96	6.30 ± 1.07	6.70 ± 0.98	6.42 ± 1.10
Second/right	6.48 ± 1.00	6.30 ± 1.12	6.75 ± 1.10	6.39 ± 1.07

Second assessment was carried out approximately 6 h after the first. Data are presented as the pupil diameter in millimeters (mean ± standard deviation). Kruskal–Wallis H test: statistical significance level of  $P < 0.05$ . No statistically significant differences were observed among the causes of brain death. CPA, cardiopulmonary arrest; SAH, subarachnoid hemorrhage.

in the following assessment. Although a few cases of brain death have involved pupils of  $\leq 3.9$  mm, this might be a rare event. We propose that such cases may involve other contributing factors, such as a lack of whole cerebral blood flow. According to the results of the present study, a pupil diameter of  $\geq 4$  mm appears to be a reasonable definition of brain death during bedside examinations. Some electrical devices were recently developed that can finely measure not only the pupil size to a 0.2-mm level of accuracy, but also the percentage change in and velocity of the constriction.<sup>13</sup> If the use of these devices becomes widespread, the criteria for brain death may change.

No mydriatic agents were used in this study, and the effect of sedative drugs used earlier for intensive care could be excluded. Pupil size fluctuates according to the balance between the actions of the pupil dilator muscle (m. dilatator pupillae), which is innervated by the sympathetic nerve, and the pupil sphincter muscle (m. sphincter pupillae), which is innervated by the oculomotor nerve. Dysfunction of the Westphal–Edinger nucleus or any blockade in the oculomotor nerve pathway results in dominance of the pupil dilator muscle over the sphincter. However, dysfunction or a blockade of the sympathetic nerve, such as occurs in Horner's syndrome, results in miosis.

In this study, we found that the pupils were not identical in size during the first and second assessments, even 6 h later. In brain death, the position of the pupil is fixed in the midposition, but the pupil size might not be fixed. This suggests some degree of imbalance between the dilator and sphincter muscles of the pupil. We cannot explain the slight changes in pupil size in cases of brain death.

## CONCLUSIONS

**I**N SUMMARY, 148 brain-dead, heart-beating organ donors in Japan were reviewed with respect to the

diagnosis of brain death by committee members delegated by the Japanese MHLW. We studied all records of the first and second assessments (6 h later) in each case. In all cases, the pupil was fixed in the midposition and lacked a light reflex. We also observed that 95% of the pupil diameters measured 4.0–8.5 mm at each evaluation with an average of 6.1 and 6.4 mm at the first and second assessments, respectively. The criteria for brain death in the USA and Japan include a pupil diameter of  $\geq 4$  mm. We have confirmed that this criterion is reasonable. However, we also found that pupil size after brain death may change in some cases by unknown mechanisms.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

**N**ONE.

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