Optimal Duration of the Apnea Test for Determining Brain Death: Benefit of the Short-Term Apnea Test

Seung Min Baik (✉ illaillailla@naver.com)

Ewha Women's University Mokdong Hospital   https://orcid.org/0000-0003-1051-6775

Jin Park

Ewha Womans University Seoul Hospital

Tae Yoon Kim

Ewha Womans University Seoul Hospital

Jung Hwa Lee

Ewha Women's University Mokdong Hospital

Kyung Sook Hong

Ewha Womans University Seoul Hospital   https://orcid.org/0000-0002-8022-5693

Research Article

Abstract

Background: The criteria for brain death determination have not been unified globally, and there is no global consensus on the apnea test, which is essential for determining brain death. Since the apnea test is associated with many complications, we aimed to determine an optimal duration of the apnea test.

Methods: We analyzed the results of the apnea test performed for brain death determination between August 2013 and February 2021 at a single institution in South Korea. Elevations in the partial pressure of carbon dioxide and mean arterial blood pressure fluctuations over time in the apnea test were recorded.

Results: In the 1st and 2nd tests, the mean partial pressure of carbon dioxide increased by more than 20 mmHg at 3 min after the apnea test compared to before the test ($P < 0.05$). At 4 min in the 1st test and 5 min in the 2nd test, the partial pressure of carbon dioxide exceeded 60 mmHg ($P < 0.05$). The fluctuation in the mean arterial blood pressure observed for 5 min during the apnea test was not significant. There was no significant fluctuation in the mean arterial blood pressure over time in the apnea test between patients with normal chest radiography findings and those with abnormal chest radiography findings ($P = 0.888$).

Conclusion: Our study proposes that a short-term apnea test protocol is valid for the preservation of organs for donation.

Background

Brain death was first described in 1959 and is defined as the irreversible loss of all identifiable brain functions, including those of the brainstem [1, 2]. Although it is an established medical concept, there is no global consensus regarding the determination of brain death [3]. According to the American Academy of Neurology (AAN) guidelines, the following criteria must be met when determining brain death: presence of an irreversible etiology; neurologically confirmed coma, loss of the brainstem reflex, and apnea test positivity; and positive optional tests (no cerebral blood flow on angiography or transcranial Doppler ultrasound [TCD], no electrical activity on electroencephalography [EEG], and no uptake of technetium on brain scan) [4].

The apnea test is essential for clinically determining brain death [4]. Its main purpose is to demonstrate the absence of a respiration control system reflex in the brainstem when stimulation of respiration occurs with an increased partial pressure of carbon dioxide ($PaCO_2$). Regarding the apnea test and positive criteria for the apnea test in South Korea [5], pre-oxygenation is first achieved with 100% oxygen (O_2) or 95% O_2 and 5% CO_2 via a mechanical ventilator for 10 min. Thereafter, the mechanical ventilator is removed, and 6 L/min of 100% O_2 is supplied through an endotracheal tube. If spontaneous respiration is not induced although $PaCO_2$ has risen to ≥ 50 mmHg as determined by blood gas analysis, the apnea test is deemed positive. The apnea test in the United States slightly differs from that in South Korea [4]. In

the United States, after removing the mechanical ventilator, there is observation for an apnea pattern for 8 to 10 minutes. Thereafter, arterial blood gas analysis (ABGA) is performed, and the apnea test is considered positive if $PaCO_2$ exceeds 60 mmHg or increases by ≥20 mmHg above the reference value. The differences between the apnea tests of the two countries mainly focus on the test duration as well as $PaCO_2$, which is a criterion for determining a positive apnea test. In Japan, the standard duration for the apnea test is unspecified, but the $PaCO_2$ is the same as in the United States [6].

A survey of 80 countries showed no agreement between continents and countries, and even within one country regarding brain death diagnostic criteria and apnea test modalities for brain death [3]. There were differences regarding existing laws and guidelines related to determining brain death, number of medical staff for the determination, observation duration, test for determination, and apnea test procedure. Factors other than the implementation patterns of the apnea test are closely related to ethical considerations. In other words, there is no global consensus on the implementation of the apnea test, although such a consensus seems necessary for patient safety. The implementation pattern of the apnea test is more closely related to the condition of the patient waiting for brain death determination. This may be due to complications of the apnea test, which include hypoxemia, hypotension, acidemia, hypercapnia, increased intracranial pressure, pulmonary hypertension, and arrhythmias [7–14]. Compared to the conventional apnea test, the modified apnea test (MAT) maintains positive end-expiratory pressure (PEEP) and can prevent lung atelectrauma and hypoxia even after mechanical ventilator removal [10]. However, MAT does not reduce other hypercapnia- and hypoxia-induced complications. These complications can result in damage to organs intended for donation. Since determining brain death is related to stopping unnecessary life support and also to organ donation, organ preservation should be considered while managing potential brain death patients for organ donation [15]. Therefore, identifying the most effective and safest apnea test method that allows the maintenance of hemodynamic stability without interfering with the brain death determination process can result in better post-transplantation outcomes.

The study aimed to suggest an appropriate apnea test duration by reviewing the records of a single institution in South Korea.

Methods

Patients and collected data

Patients who underwent brain death management for organ donation between August 2013 and February 2021 were enrolled. The most appropriate routine protocol for brain death management was implemented for all patients. The following demographic and clinical data were obtained: sex, age, cause of brain death, total duration of hospitalization, brain death management period, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, plateau pressure, norepinephrine infusion rate, and chest radiography findings. Chest radiography findings were classified into normal and abnormal findings. The abnormal findings group included one or more of the following: pneumonia,

pulmonary edema, pleural effusion, atelectasis, bronchiectasis, and emphysema. In addition, when cardiac donation was planned or cardiac function evaluation was necessary during management, echocardiography was performed, and ejection fraction (EF) values were recorded.

Apnea test protocol

The apnea test protocol used in our institution employs MAT. The apnea test to determine brain death was performed twice, at least 6 hours apart. It is a law in South Korea to perform an apnea test twice when determining brain death. Ten minutes before the apnea test, pre-oxygenation was performed with the fraction of inspired oxygen (FiO_2) set to 100%. In the presence of the attending physician, the mechanical ventilator was removed from the patient, and a bag valve mask equipped with a PEEP valve was connected. The O_2 supplied had an FiO_2 of 100% and flow rate of 6 L/min. After applying the bag valve mask to the patient, we confirmed that the patient had apnea and performed an ABGA test every minute from 1 min to 5 min or more if possible. The attending physician monitored the patient's condition during the apnea test and recorded the arterial blood pressure (ABP) and pulse rate every minute during blood sampling. When the $PaCO_2$ level met the positive criteria for an apnea test, blood sampling was stopped and a mechanical ventilator was connected. All enrolled patients met positive criteria for both apnea tests.

Statistical analysis

All numeric variables, such as age, ABGA results, and variables related to hemodynamic status, are expressed as mean ± standard deviation. Categorical variables, such as sex, cause of brain death, and chest radiography findings, were analyzed using descriptive statistics. ABGA results, serum lactate level, and hemodynamic status observed every minute, were analyzed and compared with baseline results using the paired t-test. Serial changes in $PaCO_2$ and partial pressure of oxygen (PaO_2) in the 1st and 2nd apnea tests were analyzed by one-way repeated measures analysis of variance (ANOVA). Additionally, differences in plateau pressure and norepinephrine infusion rate between the pre- and post-apnea tests were analyzed using a paired t-test. The serial effect of differences in chest radiography findings on hemodynamic status during the apnea test was analyzed by two-way repeated-measures ANOVA. The statistical analysis was conducted and graphs were created using SPSS version 26.0 (IBM, Armonk, NY, USA). Statistical significance was designated as a significance level (*P* value) less than 0.05.

Ethics

This study was approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital (approval number: EUMC 2021-02-027).

Results

Eighty-six patients who underwent the apnea test to determine brain death between August 2013 and February 2021 were enrolled in this study. Among them, 55 (64%) were men and 31 (36%) were women. The average age of the patients was 51.8 ± 13.8 years. Non-traumatic hemorrhage was the most

common cause of brain death (n=33, 38.4%). The total duration of hospitalization and the brain death management period were 14.4 ± 32.8 days and 2.8 ± 0.9 days, respectively. A mechanical ventilator was applied to all patients, and the average plateau pressure was 20.40 ± 5.33 cmH$_2$O. On chest radiography, 21 patients (24.4%) had normal findings and 65 patients (75.6%) had abnormal findings. Echocardiography was performed in 73 of the 86 enrolled patients: 16 (21.9%) and 57 (78.1%) patients had EF <50% and ≥50%, respectively. The demographic and clinical characteristics of the patients are presented in Table 1. In the 1st apnea test, 3 patients underwent the test for up to 6 min, 2 patients for up to 8 min, 1 patient for up to 9 min, and 1 patient for up to 10 min. In the 2nd apnea test, 5 patients underwent the test for up to 6 min and 1 patient for up to 7 min.

Table 1
Demographics and clinical characteristics

Variables	n = 86
Sex (male:female)	55 (64%):31 (36%)
Age (yr)	51.8±13.8
BMI (kg/m^2)	23.22±3.67
Cause of brain death	
Traumatic hemorrhage	18 (20.9%)
Non-traumatic hemorrhage	33 (38.4%)
Cerebral infarction	3 (3.5%)
Encephalitis	2 (2.3%)
Cardiac arrest	12 (14.0%)
Hanging-induced hypoxic brain injury	17 (19.8%)
Drawning-induced hypoxic brain injury	1 (1.2%)
Total length of hospitalization (days)	14.4 ±32.8
Brain death management period (days)	2.8±0.9
APACHE II score	31.6±7.1
Plateau pressure (cmH$_2$O)	20.40±5.334
Norepinephrine infusion rate (mcg/kg/min)	0.14±0.13
Chest X-ray finding	
Normal finding	21 (24.4%)
Abnormal findings[a]	65 (75.6%)
Ejection fraction on echocardiography (n=73)	
<50%	16 (21.9%)
≥50%	57 (78.1%)
BMI body mass index, *APACHE* Acute Physiologic Assessment and Chronic Health Evaluation	
[a]Abnormal findings: pneumonia, pulmonary edema, pleural effusion, atelectasis, bronchiectasis and emphysema.	

There were significant changes in pH and $PaCO_2$ levels compared to the baseline results. At 3 minutes in the 1st and 2nd apnea tests, $PaCO_2$ exceeded the baseline value by 20 mmHg ($P < 0.05$) (Table 2). There was no significant change in the mean ABP during the 5-minute apnea test. The ABGA results, hemodynamic status, and serum lactate levels observed during the apnea test are presented in Table 2.

Table 2
1st and 2nd apnea test results

Variables	Values[a]	ΔValues[a]				
ABGA	Baseline results	Δ1minute results (p value)	Δ2minute results (p value)	Δ3minute results (p value)	Δ4minute results (p value)	Δ5minute results (p value)
1st apnea test						
pH	7.323 ± 0.081	-0.066 ± 0.040 (< 0.05[*])	-0.106 ± 0.023 (< 0.05[*])	-0.138 ± 0.034 (< 0.05[*])	-0.152 ± 0.031 (< 0.05[*])	-0.166 ± 0.050 (< 0.05[*])
$PaCO_2$ (mmHg)	41.4 ± 4.2	13.01 ± 4.27 (< 0.05[*])	15.66 ± 4.36 (< 0.05[*])	20.60 ± 5.81 (< 0.05[*])	22.59 ± 6.62 (< 0.05[*])	25.18 ± 9.07 (< 0.05[*])
PaO_2 (mmHg)	327.0 ± 150.3	56.05 ± 86.74 (< 0.05[*])	-47.17 ± 103.22 (< 0.05[*])	-59.77 ± 159.35 (< 0.05[*])	-114.32 ±113.05 (< 0.05[*])	-88.89 ± 98.75 (< 0.05[*])
HCO_3 (mEq/L)	21.2 ± 3.8	2.59 ±1.91 (< 0.05[*])	2.03 ± 2.18 (< 0.05[*])	1.91 ± 1.60 (< 0.05[*])	1.41 ± 5.41 (0.137)	2.15 ± 1.89 (< 0.05[*])
SaO_2 (%)	97.9 ± 3.5	0.89 ± 2.71 (0.168)	-2.49 ± 9.74 (0.115)	-3.78 ± 7.54 (< 0.05[*])	-2.42 ± 5.64 (< 0.05[*])	-3.41 ± 9.18 (0.187)
Mean arterial blood pressure (mmHg)	97 ± 21	9.24 ± 26.12 (0.164)	4.91 ± 17.48 (0.106)	-1.61 ± 22.82 (0.635)	-10.657 ± 34.70 (0.074)	-6.62 ±30.92 (0.455)
Pulse rate (bpm)	99 ± 25	3.00 ± 6.36 (0.070)	2.34 ± 10.79 (0.208)	3.80 ± 10.02 (< 0.05[*])	4.09 ± 9.85 (< 0.05[*])	0.77 ± 11.02 (0.806)

$PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, HCO_3 bicarbonate, SaO_2 oxygen saturation

[*]*P < 0.05*

[a] Values expressed as mean ± SD.

Variables	Values[a]	ΔValues[a]				
Serum lactate level (mg/dL)	13.9 ± 7.9	0.19 ± 2.21 (0.713)	-0.59 ± 1.78 (< 0.05[*])	-1.12 ± 2.25 (< 0.05[*])	-0.90 ± 2.20 (< 0.05[*])	-1.60 ± 3.28 (0.157)
2nd apnea test						
pH	7.377 ± 0.065	-0.081 ± 0.026 (<0.05[*])	-0.111 ± 0.028 (< 0.05[*])	-0.134 ± 0.034 (< 0.05[*])	-0.149 ± 0.052 (< 0.05[*])	-0.162 ± 0.040 (< 0.05[*])
$PaCO_2$ (mmHg)	39.7 ± 3.1	11.58 ± 4.44 (< 0.05[*])	16.76 ± 6.38 (< 0.05[*])	30.29 ±69.62 (< 0.05[*])	37.72 ± 92.21 (< 0.05[*])	23.03 ± 7.87 (< 0.05[*])
PaO_2 (mmHg)	379.2 ± 186.1	30.62 ±120.06 (0.324)	-44.32 ± 111.41 (< 0.05[*])	16.03 ±462.97 (0.817)	-123.06 ± 124.21 (< 0.05[*])	-118.56 ± 208.01 (0.088)
HCO_3 (mEq/L)	23.1 ± 4.0	1.39 ± 1.71 (< 0.05[*])	2.08 ± 2.22 (< 0.05[*])	6.71 ± 31.08 (0.150)	2.18 ± 1.57 (< 0.05[*])	2.03 ± 1.90 (< 0.05[*])
SaO_2 (%)	98.7 ± 1.9	-0.28 ± 2.41 (0.624)	-1.04 ±4.76 (0.157)	-2.34 ± 7.10 (< 0.05[*])	-1.26 ± 2.51 (< 0.05[*])	-1.81 ± 4.72 (0.211)
Mean arterial blood pressure (mmHg)	96 ± 17	6.87 ± 27.22 (0.345)	4.55 ± 23.37 (0.232)	0.00 ± 26.45 (1.000)	-0.35 ± 26.11 (0.938)	-1.73 ± 26.68 (0.842)
Pulse rate (bpm)	96 ± 17	-0.33 ± 8.34 (0.879)	1.00 ± 6.25 (0.324)	2.70 ± 8.78 (0.050)	2.77 ± 6.71 (< 0.05[*])	5.56 ± 6.84 (< 0.05[*])

$PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, HCO_3 bicarbonate, SaO_2 oxygen saturation

[*]$P < 0.05$

[a] Values expressed as mean ± SD.

Variables	Values[a]	ΔValues[a]				
Serum lactate level (mg/dL)	13.3 ±8.6	-0.80 ± 1.02 (< 0.05[*])	-0.76 ± 1.62 (< 0.05[*])	-0.77 ± 1.82 (<0.05[*])	-1.13 ± 1.43 (< 0.05[*])	-0.83 ± 2.07 (0.262)

$PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, HCO_3 bicarbonate, SaO_2 oxygen saturation

[*]$P < 0.05$

[a] Values expressed as mean ± SD.

The serial analysis of $PaCO_2$ for 5 min showed that the increase in $PaCO_2$ was significant over time in the 1st and 2nd apnea tests. $PaCO_2$ exceeded 60 mmHg in 3 min in the 1st apnea test and 4 min in the 2nd apnea test ($P < 0.05$) (Fig. 1).

The serial analysis of PaO_2 for 5 min showed that in both the 1st and 2nd apnea tests, PaO_2 was elevated at 1 min of the test, but decreased thereafter. The change trend was significant in the 1st apnea test ($P < 0.05$), but not in the 2nd apnea test ($P = 0.095$) (Fig. 2).

The norepinephrine infusion rate was significantly increased between the 1st pre- and post-apnea tests (0.13 ± 0.13 µg/kg/min in the pre-apnea test vs 0.15 ± 0.13 µg/kg/min in the post-apnea test, $P < 0.05$). Except for this result, there was no significant difference in plateau pressure and norepinephrine infusion rate in the pre- and post-apnea tests (Table 3).

Table 3
Plateau pressure and norepinephrine infusion rate of pre- and post-apnea test

Variables	Values	*p* value
1st apnea test		
Plateau pressure (cmH$_2$O)		
Pre-apnea test	20.66±5.24	0.072
Post-apnea test	22.72±6.16	
Norepinephrine infusion rate (mcg/kg/min)		
Pre-apnea test	0.13±0.13	< 0.05[*]
Post-apnea test	0.15±0.13	
2nd apnea test		
Plateau pressure (cmH$_2$O)		
Pre-apnea test	22.76±6.17	0.397
Post-apnea test	22.42±5.95	
Norepinephrine infusion rate (mcg/kg/min)		
Pre-apnea test	0.09±0.10	0.120
Post-apnea tes	0.09±0.11	
[*]*P* < 0.05		

Subgroup analysis was also performed. Changes in mean ABP during the apnea test were compared between the normal and abnormal finding groups on chest radiography, and there was no significant difference between the two groups ($P = 0.888$) (Fig. 3).

Discussion

This study analyzed the results of apnea tests conducted by a single institution in South Korea and suggests a rational and unified international guide to the apnea test protocol.

According to the results, PaCO$_2$ exceeded 60 mmHg in ABGA within 4 min of starting the apnea test (Figs. 1 and 2). This result met the positive criteria for the apnea test suggested by the AAN guidelines. In this study, the increase in PaCO$_2$ over time was significant within 5 min. The short-term apnea test is considered an essential test for brain death determination.

Elevation of $PaCO_2$ causes an additional increase in intracranial pressure in patients with potential brain death, as well as complications such as weakening of myocardial contractility, arrhythmias, and respiratory acidosis [16]. According to a review of apnea test complications reported in 2013, hypotension was observed in 111 (18%) of 608 patients who underwent the test [17]. However, maintaining proper blood pressure in the management of brain death is important to prevent ischemic changes in organ(s) for donation and to increase transplant success rates. Therefore, according to the AAN guidelines, the systolic blood pressure should be ≥ 100 mmHg and the mean ABP should be ≥ 60 mmHg before starting the apnea test for brain death determination. In this study, we aimed to maintain a mean ABP of ≥ 65 mmHg before the apnea test and during the entire management period. In fact, the pH from the ABGA during or immediately after the apnea test decreased significantly over time. There were no significant differences in the mean ABP and pulse rate over time. Cardiovascular dysfunction, which is a common complication during the short-term apnea test and lasted for 1 to 5 minutes, was not severe. Therefore, a short apnea test should be considered for safer outcomes.

The vasopressor infusion rate was significantly increased between the 1st pre- and post-apnea tests. However, the increase in vasopressor infusion rate in the 1st apnea test was as small as 0.02 μg/kg/min. According to the brain death management protocol of our institution, we checked the mean ABP before the apnea test and, in some cases, preemptively increased the vasopressor injection rate when a borderline mean ABP of approximately 65 mmHg was observed. Therefore, it might have acted as a bias due to the external factors of the study. In addition, it is possible that these results were observed because fluid resuscitation was not sufficiently administered to manage potential brain death patients before the 1st apnea test for brain death determination. In fact, the increase in vasopressor infusion rate was not significant between the 2nd pre- and post-apnea tests.

During the apnea test, there was no significant difference in mean ABP fluctuations between the normal and abnormal finding groups on chest radiography; therefore, a short-term apnea test seems safe even in patients with poor lung conditions.

MAT is a method for preventing lung damage without affecting hypercapnia by maintaining PEEP even after removing the mechanical ventilator from the patient [11, 18]. In the 1st apnea test in this study, PaO_2 was significantly changed every minute, but its value was ≥ 90 mmHg (Table 2). Previous studies have confirmed that MAT did not negatively affect apnea test results and allowed a safer completion of the tests [19, 20]. MAT was also performed in the present study. Changes in plateau pressure in the pre- and post-apnea tests were checked as a parameter to confirm the presence or absence of lung damage, and no significant changes were observed. Changes in plateau pressure disproved the changes in lung compliance. Although the degree of change was not significant in this study, if the duration of the apnea test is prolonged, lung compliance may worsen. If lung donation is planned, caution is required during the apnea test.

If a normal body temperature is maintained and there is no lung disease, only 5 min of apnea can raise $PaCO_2$ from 40 mmHg to 60 mmHg [21]. Nevertheless, a global consensus has not yet been reached.

Although the apnea test in South Korea can be considered to be a relatively weak standard compared to the AAN guideline, EEG is mandatory for all brain death determinations, and TCD is also performed in some cases. However, according to the AAN guidelines and a publication by the World Brain Death Project in 2020, EEG was excluded from the mandatory tests because of its high false-positive rate; however, it could be performed as an optional test if the apnea test is unavailable [4, 22]. TCD, which is not an essential test for brain death determination, can also be performed as an optional test if the apnea test is infeasible. The sensitivity and specificity of TCD for determining brain death are 90% and 98%, respectively [23]. The additional use of TCD may help shorten the duration of the apnea test in brain death determination.

In a previous study, we attempted to determine the optimal duration of the apnea test by performing ABGA every minute during the apnea test [10]. In that study, $PaCO_2$ exceeded 60 mmHg 4 min after the removal of the mechanical ventilator; thus, it can be considered that observing the patient's apnea pattern for at least 8 min during the apnea test, as presented by the AAN guidelines, is relatively long. Although many studies have reported that complications such as hemodynamic instability and lung damage can be caused by the apnea test, studies on the possible shortening the apnea test duration are insufficient. The reason may be because of the recognition that more stringent criteria should be applied because the apnea test is valuable as an essential test for brain death determination.

A study of guidelines for brain death in 80 countries found that detailed guidelines were inconsistent, and in the U.S., there was no internal agreement because of differences in laws even between states [3]. Likewise, the implementation patterns of the apnea tests and positivity criteria have not been standardized worldwide. It will be difficult to achieve a consensus regarding the criteria for brain death determination because of differences in legal systems, culture, and medical standards between countries. Nevertheless, for the safety of patients waiting for brain death determination and for organ preservation after brain death determination, there is a need for a global consensus on the implementation pattern of the apnea test, which is generally considered essential in brain death determination. We suggest an optimal apnea test protocol as follows: 1) after removing the mechanical ventilator from the patient, observe the patient's apnea patterns for 5 min; 2) after 5 min, perform the short-term ABGA for 1 or 2 min; and 3) when it is confirmed that $PaCO_2$ exceeds 60 mmHg, terminate the apnea test immediately.

Because this study was conducted in a single institution, the apnea test was not performed on patients of various races, physiques, etc. This is an important limitation with regarding to generalizing our findings. A global multicenter study is necessary to establish a reasonable apnea test that can be widely performed worldwide.

Conclusion

In conclusion, when brain death was determined, MAT for approximately 5 min resulted in a sufficient increase in $PaCO_2$, meeting the positive criteria for the apnea test, and hemodynamic instability during

the test was not significant. This study should be valuable for providing guidelines for a globally relevant optimal duration for the apnea test.

Declarations

Acknowledgments

Authors' contributions

KSH contributed to the conception of the study. The manuscript was drafted by SMB and revised by all authors. JP, TYK and JHL collected data. KSH and SMB designed and conducted the statistical analysis. All authors critically reviewed the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of work.

Funding

Availability of data and materials

All data associated with this manuscript are included in the main text and supplementary materials.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital (approval number: EUMC 2021-02-027).

Consent for publication

All authors have read the manuscript and consented for this manuscript to be published by Critical Care.

Competing interests

The authors declare that they have no competing interests.

References

1. (1995) Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 45: 1012–1014. https://doi.org/10.1212/WNL.45.5.1012

2. Wertheimer P, Jouvet M, Descotes J (1959) [Diagnosis of death of the nervous system in comas with respiratory arrest treated by artificial respiration]. Presse Med 67: 87–88

3. Wijdicks EF (2002) Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 58: 20–25. https://doi.org/10.1212/WNL.58.1.20

4. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM, American Academy of N (2010) Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 74: 1911–1918. https://doi.org/10.1212/WNL.0b013e3181e242a8

5. Korean Network for Organ Sharing. Available from: https://www.konos.go.kr/konosis/index.jsp.

6. Japan Organ Transplant Network. Available from: https://www.jotnw.or.jp/files/page/medical/manual/doc/guidelines.pdf.

7. Wijdicks EF, Rabinstein AA, Manno EM, Atkinson JD (2008) Pronouncing brain death: Contemporary practice and safety of the apnea test. Neurology 71: 1240–1244. https://doi.org/10.1212/01.wnl.0000327612.69106.4c

8. Schafer JA, Caronna JJ (1978) Duration of apnea needed to confirm brain death. Neurology 28: 661–666. https://doi.org/10.1212/WNL.28.7.661

9. Saposnik G, Rizzo G, Vega A, Sabbatiello R, Deluca JL (2004) Problems associated with the apnea test in the diagnosis of brain death. Neurol India 52: 342–345

10. Park J, Lee YJ, Hong KS (2019) Proposed safe apnea test using positive end-expiratory pressure valve and short-term blood gas analysis: Observational study. Medicine (Baltimore) 98: e15602. https://doi.org/10.1097/MD.0000000000015602

11. Levesque S, Lessard MR, Nicole PC, Langevin S, LeBlanc F, Lauzier F, Brochu JG (2006) Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Crit Care Med 34: 2213–2216. https://doi.org/10.1097/01.CCM.0000215114.46127.DA

12. Jeret JS, Benjamin JL (1994) Risk of hypotension during apnea testing. Arch Neurol 51: 595–599. https://doi.org/10.1001/archneur.1994.00540180073016

13. Goudreau JL, Wijdicks EF, Emery SF (2000) Complications during apnea testing in the determination of brain death: predisposing factors. Neurology 55: 1045–1048. https://doi.org/10.1212/WNL.55.7.1045

14. Benzel EC, Mashburn JP, Conrad S, Modling D (1992) Apnea testing for the determination of brain death: a modified protocol. Technical note. J Neurosurg 76: 1029–1031. https://doi.org/10.3171/jns.1992.76.6.1029

15. Goila AK, Pawar M (2009) The diagnosis of brain death. Indian J Crit Care Med 13: 7–11. https://doi.org/10.4103/0972-5229.53108

16. Price HL (1960) Effects of carbon dioxide on the cardiovascular system. Anesthesiology 21: 652–663. https://doi.org/10.1097/00000542-196011000-00009

17. Scott JB, Gentile MA, Bennett SN, Couture M, MacIntyre NR (2013) Apnea testing during brain death assessment: a review of clinical practice and published literature. Respir Care 58: 532–538. https://doi.org/ 10.4187/respcare.01962

18. Hocker S, Whalen F, Wijdicks EF (2014) Apnea testing for brain death in severe acute respiratory distress syndrome: a possible solution. Neurocrit Care 20: 298–300. https://doi.org/ 10.1007/s12028-013-9932-0

19. Ahlawat A, Carandang R, Heard SO, Muehlschlegel S (2016) The Modified Apnea Test During Brain Death Determination: An Alternative in Patients With Hypoxia. J Intensive Care Med 31: 66–69. https://doi.org/ 10.1177/0885066615599086

20. Busl KM, Lewis A, Varelas PN (2021) Apnea Testing for the Determination of Brain Death: A Systematic Scoping Review. Neurocrit Care 34: 608–620. https://doi.org/ 10.1007/s12028-020-01015-0

21. Rudolf J, Haupt WF, Neveling M, Grond M (1998) Potential pitfalls in apnea testing. Acta Neurochir (Wien) 140: 659–663. https://doi.org/ 10.1007/s007010050160

22. Greer DM, Shemie SD, Lewis A, Torrance S, Varelas P, Goldenberg FD, Bernat JL, Souter M, Topcuoglu MA, Alexandrov AW, Baldisseri M, Bleck T, Citerio G, Dawson R, Hoppe A, Jacobe S, Manara A, Nakagawa TA, Pope TM, Silvester W, Thomson D, Al Rahma H, Badenes R, Baker AJ, Cerny V, Chang C, Chang TR, Gnedovskaya E, Han MK, Honeybul S, Jimenez E, Kuroda Y, Liu G, Mallick UK, Marquevich V, Mejia-Mantilla J, Piradov M, Quayyum S, Shrestha GS, Su YY, Timmons SD, Teitelbaum J, Videtta W, Zirpe K, Sung G (2020) Determination of Brain Death/Death by Neurologic Criteria: The World Brain Death Project. JAMA 324: 1078–1097. https://doi.org/ 10.1001/jama.2020.11586

23. Chang JJ, Tsivgoulis G, Katsanos AH, Malkoff MD, Alexandrov AV (2016) Diagnostic Accuracy of Transcranial Doppler for Brain Death Confirmation: Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol 37: 408–414. https://doi.org/ 10.3174/ajnr.A4548
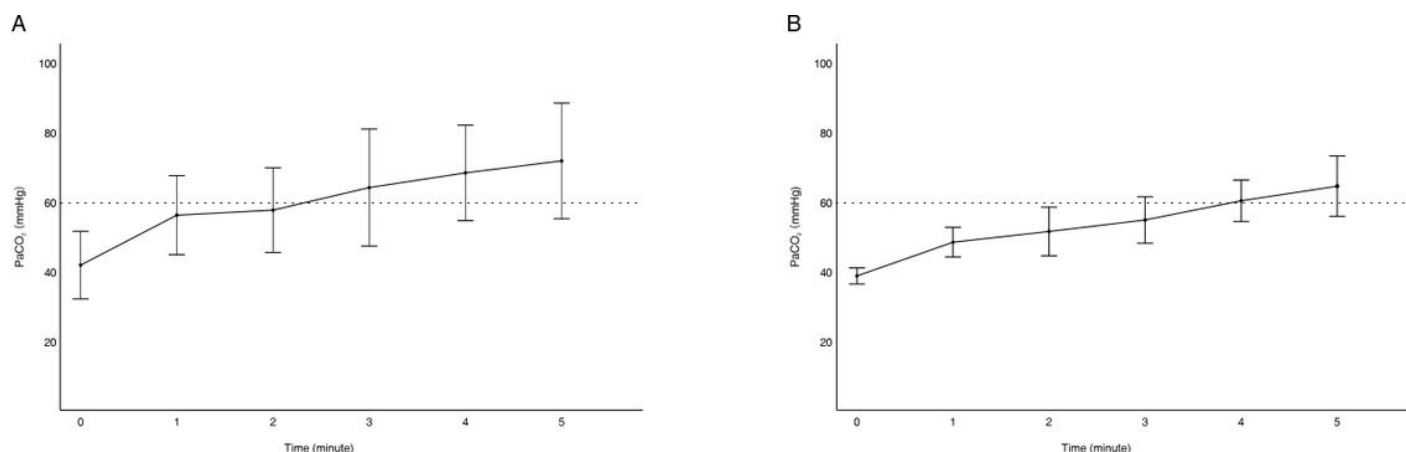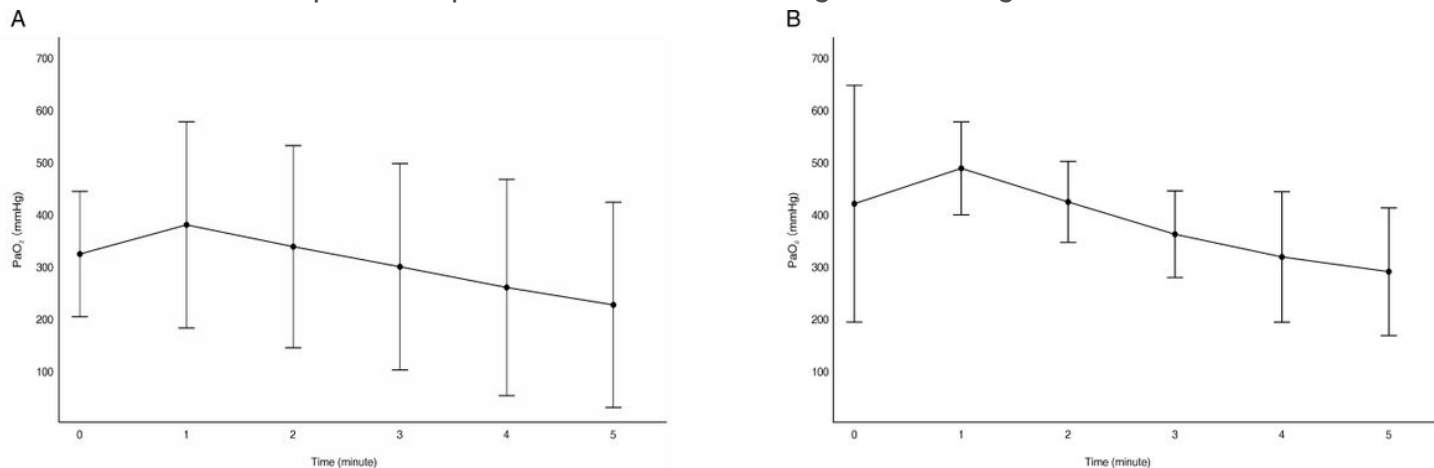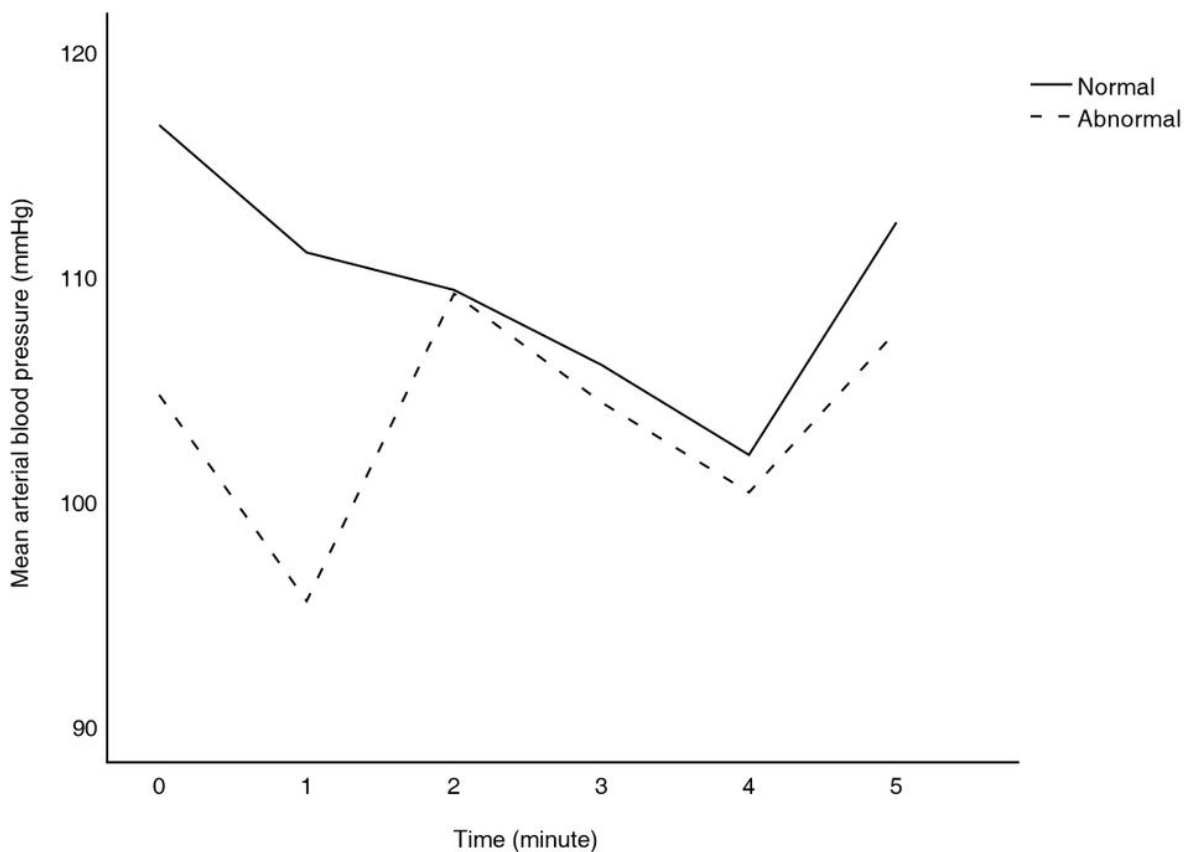
Figures

Figure 1

Increase in the partial pressure of carbon dioxide (PaCO2) in the apnea test. Panel A shows at 3 min in the 1st apnea test, the PaCO2 level was above 60 mmHg. Panel B shows at 4 min in the 2nd apnea test, the PaCO2 level was above 60 mmHg. The apnea test positive criterion is PaCO2 > 50 mmHg in South Korea, and PaCO2 > 60 mmHg according to the American Academy of Neurology (AAN) guidelines. The dotted line denotes the apnea test positive criterion according to the AAN guidelines.

Figure 2

Serial change in partial pressure of oxygen (PaO2). Panel A shows serial changes in PaO2 were significant in the 1st apnea test (P < 0.05). Panel B shows serial changes in PaO2 were not significant in the 2nd apnea test (P = 0.095).

Figure 3

Difference in mean arterial blood pressure fluctuation during the apnea test according to chest radiography findings. The difference in mean arterial blood pressure fluctuations between the two groups was not significant (P = 0.888).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistv4combined1.docx