Prediction of Apnea Testing Duration to Ensure Safety During Brain Death Assessment

Katsuyuki Sagishima, Kazutaka Oda, and Yoshihiro Kinoshita

BACKGROUND: Apnea testing is the last step of brain death assessment. This study aimed to determine whether apnea testing is safer when performed over a shorter duration. METHODS: The medical records of 200 brain-dead donors were retrospectively evaluated. All the records were anonymously registered in the Japanese Ministry of Health, Labor, and Welfare from 1999 to 2012. The rate of P_{aCO_2} increase was analyzed to calculate the duration required for apnea testing. RESULTS: At baseline, body temperature and P_{aO_2} significantly affected the increase rate of P_{aCO_2}. At baseline, the apnea testing durations were 4.7 min with normal body temperature and higher P_{aO_2} (P_{aCO_2} 40–60 mm Hg, body temperature 36.5°C, P_{aO_2} 400 mm Hg); further, it was 3.0 min with higher body temperature and lower P_{aO_2} at baseline (P_{aCO_2} 40–60 mm Hg, body temperature 38.0°C, P_{aO_2} 100 mm Hg). CONCLUSIONS: The specific duration of apnea testing during brain death assessment may be predicted by measuring the increase rate of P_{aCO_2}.
Key words: apnea; brain death; diagnostic tests; hypoxemia; hypotension; organ procurement; tissue procurement. [Respir Care 2021;66(5):793–797.

Introduction

Apnea testing is a crucial determinant in brain death diagnosis; however, it can be an invasive procedure. Although most apnea testing procedures can be safely performed with intensive monitoring, it can lead to complications, including hypotension, hypoxemia, and acidemia.[1-3] The Japanese Society of Anesthesiology Guidelines for the Implementation of Apnea Test (https://anesth.or.jp/files/pdf/guideline_MukokyuTest.pdf, *Accessed March 1, 2020*) specify that apnea testing should be continued until the P_{aCO_2} reaches 60 mm Hg. However, apnea testing duration seems unpredictable.[4-7] Calculating the increase in P_{aCO_2} during apnea testing could allow for greater control and a shorter testing period, thus improving patient safety. However, this topic has not been studied. Therefore, we aimed to test the hypothesis that apnea testing would be safer if performed over a shorter duration and may prevent complications such as hypoxemia and hypotension.

Methods

We reviewed 200 consecutive cases of individuals who experienced brain death and had donated their organs between 1999 and 2012 (Table 1). Data were obtained from the Japanese Ministry of Health, Labor, and Welfare (MHLW), Summary of Verification Meeting on Cases of Organ Donation under Brain Death (https://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/kenkou/zouki_ishoku/dl/200_matome.pdf, *Accessed March 1, 2020*) and included records from medical institutions in Japan. These institutions reported sufficient systems for organ donation, as confirmed by the MHLW. The results of blood gas analysis during apnea testing were recorded to allow calculation of the increase rate of the P_{aCO_2}. For all subjects with brain death, we reviewed data regarding blood gas levels at baseline and at subsequent 2- to 3-min intervals until P_{aCO_2} levels reached 60 mm Hg.

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The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.08366

Modeling and Simulations to Analyze the Increase in P_{aCO_2}

We attempted to model how P_{aCO_2} increases using nonlinear mixed-effects modeling software (NONMEM 7.3, ICON, Dublin, Ireland). We assumed that the increase ratio of P_{aCO_2} in the structure models was as follows:

$$P_{aCO_2,t} \text{ increase ratio } = P_{aCO_2,t}/P_{aCO_2,baseline}$$

$$P_{aCO_2,t} \text{ increase ratio } = exp^{kt} \quad \text{(A)}$$

$$P_{aCO_2,t} \text{ increase ratio } = \left(\frac{E_{max}^{Hill}}{EC_{50}^{Hill} + t^{Hill}}\right) \quad \text{(B)}$$

where equation A assumes a first-order increasing model, whereas equation B assumes a sigmoid E_{max} model. $P_{aCO_2,t}$ is the P_{aCO_2} at time t after apnea testing initiation (mm Hg), k is the P_{aCO_2} increasing rate constant (/min), t is the time after apnea testing initiation (min), E_{max} is the maximum P_{aCO_2} (mm Hg), EC_{50} is the time after apnea testing initiation required to reach half the P_{aCO_2} ratio up to E_{max} (min), and Hill is the sigmoid curve shape. We chose the simplest and most visually appropriate model of the 2 models, with the objective function value (a lower value is better for fitting the observation) being calculated during the NONMEM analysis. The exponential distribution assigned the inter-individual variability.

Next, we explored covariates that affect the increase ratio of P_{aCO_2}. Available individual data included age, sex, P_{aO_2}, body temperature, systolic blood pressure, diastolic blood pressure, pupil diameters, and auditory brainstem response test results. The Pearson test was used to determine the significance of the correlation of continuous variables with the P_{aCO_2} increasing rate constant. Here, variables with a correlation coefficient > 0.2 and $P < .05$ were considered as potential covariates. The significance of the categorical variables was examined using the Fisher exact test, with $P < .05$ indicating potential covariates. Next, we developed single-covariate models using potential covariates during the forward inclusion steps. Continuous and categorical variables were modeled for allometry and power, respectively. Based on the theory that objective function values follow a chi-square distribution, a reduction in the objective function value by $>$ 3.84 can serve as a reference for significance ($P < .05$) when a potential covariate is included. Subsequently, a full model was developed using potential significant covariates during the forward inclusion steps. The best model was finalized by testing the full model through backward elimination, where each covariate that increased the objective function value by 6.63 ($P > .01$) upon removal was eliminated.

The P_{aCO_2} increase ratio was simulated for each representative value identified as a covariate in the final model using R 3.6.1 (R, Vienna, Austria).

QUICK LOOK

Current knowledge

Apnea testing is often safely performed with intensive monitoring; however, complications such as hypotension, hypoxemia, and acidemia can occur. So far, apnea testing duration has been considered unpredictable.

What this paper contributes to our knowledge

Apnea testing duration may be predicted using a calculation based on the baseline body temperature and P_{aO_2} level, which are correlated with the increase rate of P_{aCO_2}. Predicting the duration of apnea testing may reduce unnecessarily prolonged apnea testing procedures that result in severe complications that compromise organ donation.

Standard Protocol and Subject Consent

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The institutional review board of the Kumamoto University Hospital

Table 1. Causes of Brain Death in Japanese Subjects: 1999–2012

Cause of Brain Death	Frequency (%)	Male/Female (% Males)	Age, y	P_{aO_2} at Baseline, mm Hg	Systolic Blood Pressure at Baseline, mm Hg
Subarachnoid hemorrhage	82 (41.0)	39/43 (47.6)	50 (42–56)	404 (316–476)	127 (111–148)
Head injury	35 (17.5)	25/10 (71.4)	41 (26–51)	415 (322–527)	130 (104–146)
Anoxic encephalopathy	44 (22.0)	21/23 (47.7)	42 (30–52)	392 (293–473)	113 (109–131)
Cerebral hemorrhage	31 (15.5)	23/8 (74.2)	56 (43–64)	309 (185–496)	121 (110–162)
Cerebral infarction	6 (3.0)	5/1 (83.3)	60	477 (448–505)	110 (109–126)
Brain tumor	2 (1.0)	0/2 (0.00)	27, 32*	494, 566*	98, 166*
Total	200 (100)	113/87 (56.5)	47 (37–57)	404 (289–504)	124 (109–146)

Data are presented as *n* (%) or median (interquartile range). $N = 200$ patients.
* Personal values of 2 patients are presented.

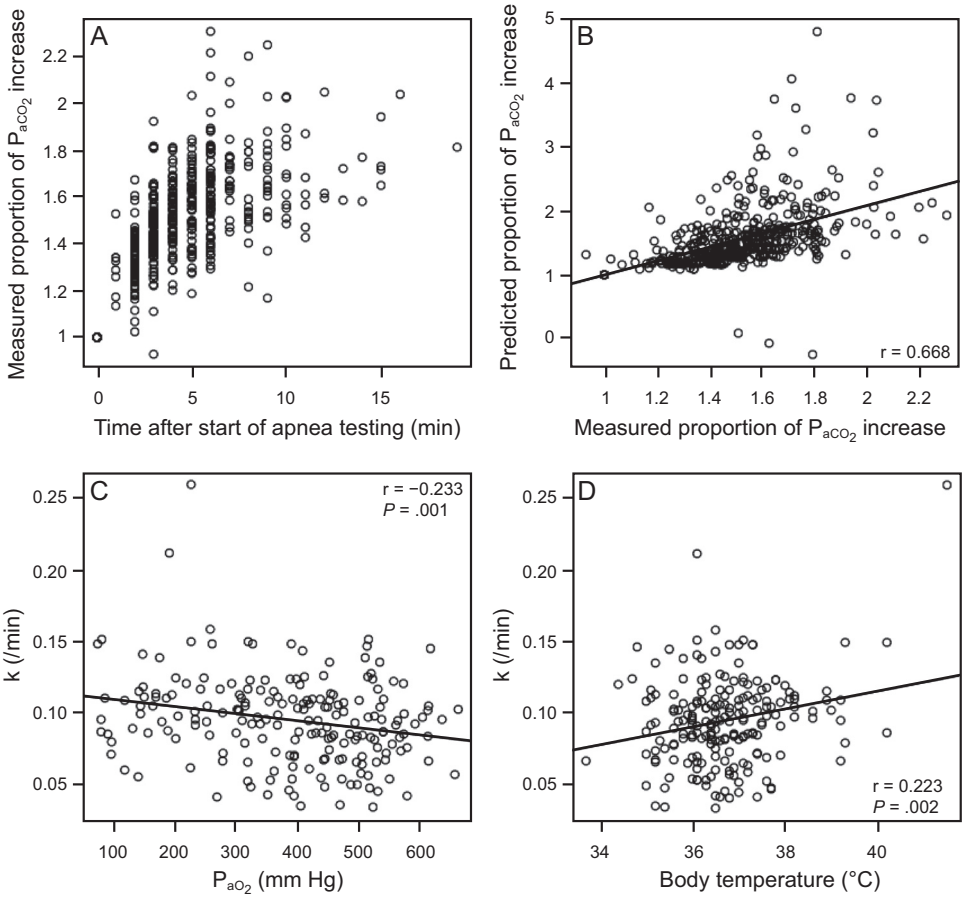

Fig. 1. Models for predicting P_{aCO_2} increase. (A) Measured proportion of the P_{aCO_2} increase across time intervals. (B) Correlation between the measured proportion and predicted proportion of the P_{aCO_2} increase. (C) Correlation between the measured P_{aO_2} and P_{aCO_2} increasing constant (*k*). (D) Correlation between body temperature and the increasing constant (*k*).

waived the need for informed consent given the retrospective nature of this study. Data obtained from the Japanese MHLW lacked identifying patient information. Furthermore, subject data will not be shared because the Japanese MHLW provided exclusive permission for this study to use the data for analyses.

Results

Development of the Final Model

Structure model A (exponential model) was used because the objective function value was 1963.496, whereas that of model B (sigmoid E_{max} model) was 3546.420. Subsequently, the potential covariates were tested, with baseline P_{aO_2} and temperature at initiation meeting the criteria for developing a full model. Although the significance of other covariates was investigated during the backward elimination step, these 2 covariates remained the most significant. Next, a final model was determined for the increase in P_{aCO_2} (Fig. 1). Baseline P_{aO_2} and body temperature were significant factors, with a lower baseline P_{aO_2} and higher baseline body temperature (Fig. 1) being significantly correlated with a greater increase in the P_{aCO_2} rate during apnea testing. The following regression equation for predicting the necessary apnea testing duration was developed:

$$\ln(P_{aCO_2}\ \text{increase ratio}) = 0.0863 \times \text{duration} \times (\text{body temp}/36.5)^{2.09} \times (P_{aO_2}/400)^{-0.16}$$

where duration (in min) = $\ln(P_{aCO_2}$ increase ratio$)/[0.0863 \times$ (body temp/36.5)$^{2.09} \times (P_{aO_2}/400)^{-0.16}]$ and P_{aCO_2} increase ratio = $P_{aCO_2-finished}/P_{aCO_2-baseline}$. Here, $P_{aCO_2-finished}$ refers to the P_{aCO_2} level at the end of apnea testing, and $P_{aCO_2-baseline}$ refers to the baseline P_{aCO_2} level; body temperature is in degrees Celsius.

All P_{aCO_2} levels were measured in mm Hg. Figure 2 describes the mean values and their corresponding 64% prediction intervals. The time required for P_{aCO_2} to increase from 40 mm Hg to 60 mm Hg (P_{aCO_2} increase

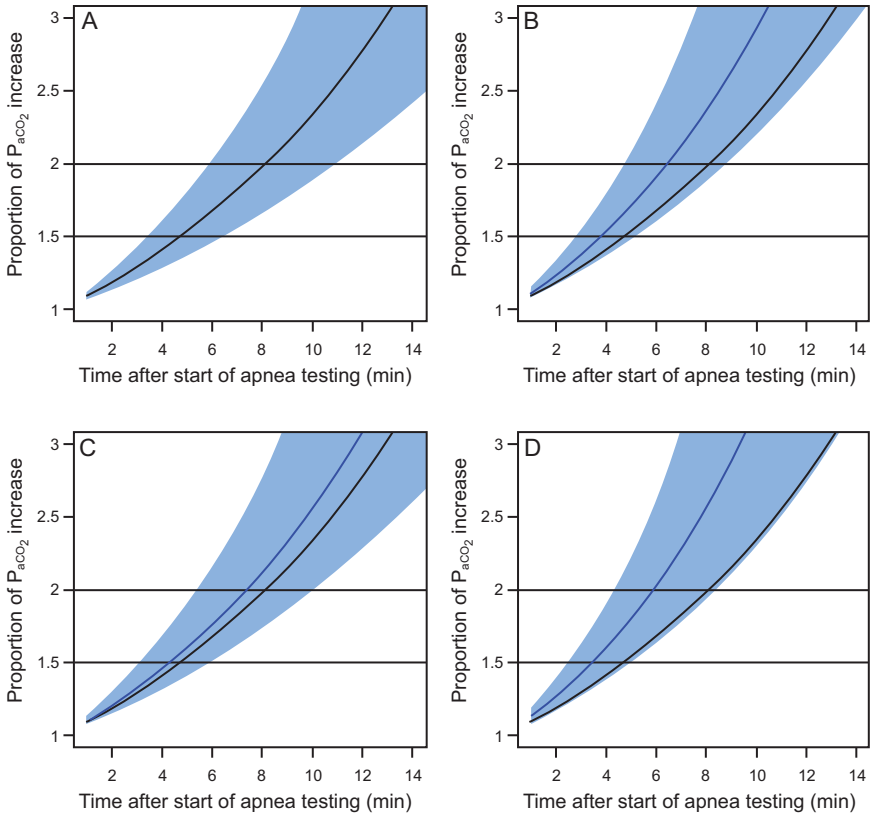

Fig. 2. Predicted proportion of P_{aCO_2} increase at representative temperatures and P_{aO_2} values at the start of apnea testing. The black curve is the predicted curve for a body temperature of 36.5°C and P_{aO_2} of 400 mm Hg at baseline (A). Blue curves and shaded areas show predicted curves and corresponding 64% prediction intervals, respectively, of the representative values indicated in each figure (B, for a body temperature of 36.5°C and P_{aO_2} of 100 mm Hg at baseline; C, for a body temperature of 38.0°C and P_{aO_2} of 400 mm Hg at baseline; D, for a body temperature of 38.0°C and P_{aO_2} of 100 mm Hg at baseline).

ratio = 1.5) at 4 representative values (with 64% prediction intervals) of temperature and P_{aO_2} at apnea testing initiation were 4.7 min (3.4–6.4; Fig. 2A), 3.8 min (2.8–5.2; Fig. 2B), 4.3 min (3.2–6.0; Fig. 2C), and 3.0 min (64% PI: 2.5–4.8; Fig. 2D).

Discussion

Apnea testing, which is necessary for brain death assessment, can be invasive. Therefore, quick termination of apnea testing after fulfilling the test criteria would be preferred. Herein, a formula was developed to calculate the minimum apnea testing duration. During most brain death assessments, apnea testing is completed within 8–10 min.[5,6] However, the Summary of Verification Meeting on Cases of Organ Donation under Brain Death from the Japanese MHLW (https://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/kenkou/zouki_ishoku/dl/200_matome.pdf, *Accessed March 1, 2020*) indicates that apnea testing is typically completed within 6 min (mean duration = 5.7 min). However, the American Academy of Neurology[8] and Japanese guidelines[9] differ with respect to when to start and repeat blood gas analyses during apnea testing. Specifically, the American and Japanese guidelines stipulate starting after 8 min and after 2 or 3 min, respectively. Furthermore, the American Academy of Neurology guidelines do not indicate a repeat interval, whereas the Japanese guidelines indicate a repeat interval of 2 or 3 min after initiation.

Similarly, there appears to be a discrepancy in the mean P_{aCO_2} increase. Global measurements[10] range between 2.5 and 3.0 mm Hg/min; however, the Results and Problems in Brain Death Assessment in Japan (https://www.jstage.jst.go.jp/article/jst/48/2-3/48_89/_pdf, *Accessed March 1, 2020*) indicated that the average was 4.7 mm Hg/min. This discrepancy could be attributed to the inverse relationship between the mean P_{aCO_2} increase and apnea testing duration. The precise P_{aCO_2} increase appears to be nonlinear[5] and unpredictable.[7] Another report identified possible variations in the P_{aCO_2} increase and stated that it was associated with factors including baseline P_{aCO_2}, oxygen flow delivery, and body temperature.[5] Among these factors, oxygen flow delivery is usually fixed at 6 L/min. In the formula we developed, the increase ratio of the P_{aCO_2} was defined as the P_{aCO_2} value at the end of the testing period

divided by the baseline P_{aCO_2}. Because body temperature and baseline P_{aO_2} may significantly affect the increase rate of the P_{aCO_2}, the testing duration may be shortened by both higher body temperature and lower P_{aO_2} at baseline.

Higher body temperatures could be assumed to boost the P_{aCO_2} increase due to increased CO_2 production during metabolism. However, the mechanism underlying the effect of baseline P_{aO_2} on apnea testing duration remains unclear. In this study, individuals who demonstrated no increase in baseline P_{aO_2} after preoxygenation with 100% oxygen could have developed moderate or severe lung injury.[11] Severely injured lungs may have reduced gas exchange and impaired CO_2 removal. Using an oxygen insufflation method, Kramer et al[12] reported that oxygen flow through a catheter to the endotracheal tube eliminated CO_2. Therefore, for individuals with impaired CO_2 removal, the P_{aCO_2} increase could be higher and apnea testing can be terminated earlier.

The retrospective design of this study, as well as the use of restricted data that are not publicly available, limited our ability to determine the precise lung diseases possibly associated with baseline P_{aO_2}. This can be explored in future studies. Moreover, we have not confirmed the validity and reliability of our formula for predicting the apnea testing duration during brain death assessment. However, we hope to do so in future studies.

We believe that predicting the necessary minimum duration of apnea testing could reduce the strain on practitioners who perform apnea testing and help preserve vital organs for donation. Specifically, predicting the apnea testing duration may reduce the chance of unnecessarily prolonged apnea testing procedures, which can cause potential complications, including hypotension, hypoxemia, and acidemia.

Conclusions

Specific apnea testing durations during assessment of brain death may be predicted by measuring the rate of increase in P_{aCO_2}. Furthermore, the minimum apnea testing duration may be predicted using a calculation based on the baseline body temperature and P_{aO_2} level, which are correlated with the rate of increase in P_{aCO_2}.

ACKNOWLEDGMENTS

The authors thank the Japanese Ministry of Health, Labour, and Welfare for providing the data used for this study. The authors also thank Kazutaka Oda PhD, of Kumamoto University Hospital, Department of Pharmacy, for conducting the statistical analysis. Finally, the authors thank Editage (www.editage.com) for English language editing.

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