Identification of Hemodynamic Risk Factors for Apnea Test Failure During Brain Death Determination

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ABSTRACT

Objective. An apnea test is essential step for diagnosing brain death and is known to be relatively safe. However, various complications such as hypoxia, arrhythmias, and hypotension could occur. Herein, we identified risk factors of failed apnea test and determined their optimal cutoff values.

Methods. We retrospectively analyzed 512 patients of apnea test to diagnose brain death and classified them into 2 groups according to success or failure of the test. Demographic characteristics, value of arterial blood gas analysis, and systolic blood pressure (SBP) were collected, and alveolar-arterial gradient (A-a gradient) and Pao_2/fraction of inspired oxygen ratio were calculated to evaluate the respiratory status.

Results. A total of 484 patients completed the apnea test, and the test was aborted in 28 patients because of hypotension or refractory hypoxemia. The SBP, pH, Pao_2, and Pao_2/fraction of inspired oxygen ratio were higher in success group, whereas A-a gradient was lower. In multivariate analysis, low SBP (odds ratio [OR], 0.976; 95% CI, 0.958–0.994; $P = .01$), low pH (OR, 0.004; 95% CI, 0.000–0.184; $P = .005$), and elevated A-a gradient (OR, 1.005; 95% CI, 1.003–1.008; $P = .001$) were associated with apnea test failure. The optimal cutoff values to predict the test failure were 105.0 mm Hg for pretesting SBP, 7.326 for pretesting pH, and 556.4 mm Hg for pretesting A-a gradient.

Conclusion. Early recognition and aggressive management for the risk factors are important to reduce failure rates of apnea test and consequently improve outcomes of organ procurement.

ORGAN transplant has been considered to be the optimal treatment for patients with end-stage organ disease in spite of a critical shortage of donated organs [1]. Despite the striving for increasing organ donation, the persistent shortage of donors and donated organs transplanted per donor continue, while the number of patients on waiting lists outweighs the number of organs available. To resolve this problem with organ shortage, early recognition of potential donors and proper donor management play an important role in increasing organ procurement rates and improving the quality of these organs [2].

The apnea test is one of the essential steps for diagnosing brain death and is known to be relatively safe [3]. However, many potential organ donors are transferred to the donor management team in the status of hemodynamic instability usually accompanied with severe metabolic acidosis, hypoxia, or electrolyte imbalance [4]. Although duration of the test is short and safety of apnea test has improved with appropriate precautions, various complications, such as hypoxia, dysrhythmias, and hypotension, could occur during the test. About 10% of donor patients could not complete the apnea test because of these fatal complications. [3,5] Therefore, we suggest decreasing failure rate by identifying the risk factors of the apnea test would be necessary to

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increase the number of transplants and improve outcomes through proper management of potential donors. However, there have been only small-sized studies analyzing the risk factors for apnea test failure, although the hemodynamic or pulmonary instability during apnea test would cause critical hypoperfusion of vital organs, which has an impact on the organ procurement rates [6].

The aim of this study is to identify the risk factors of failed apnea test and determine the optimal cutoff value of the risk factors of failed apnea test.

METHODS

Study approvals were obtained from the Institutional Review Board of St. Mary's Hospital, Seoul (No. IRB; KC18RESIO300).

Patients

From January 2011 to December 2017, all potential brain dead patients who had the apnea test to confirm brain death for organ donation from 17 to 74 years old were retrospectively reviewed using the electronic medical records and operation records. Patients with insufficient data or medical records and patients who died during the donor management or were dead on arrival were excluded from analysis.

Apnea Test

An apnea test was performed in cases of all brain stem reflexes when light reflexes, corneal reflexes, caloric responses, gag reflex, and coughing in response to tracheal suctioning were absent without significant confounding factors, such as unresuscitated shock, hypothermia (defined as a body temperature less than 34°C), severe metabolic disturbances, evidence of drug intoxication, poisoning, or the use of neuromuscular-blocking agents [1,7] All patients received mechanical ventilation support via an endotracheal tube, and their blood pressure was monitored continuously through the catheter inserted into the radial artery. Before the apnea test, arterial blood gas value was obtained to determine basal $Paco_2$ less than 40.0 mm Hg. An external warming device was used to maintain normal or near normal temperature (>36°C). In accordance with the practical guidance of American Academy of Neurology, all patients were preoxygenated with 100% oxygen for 10 minutes before the initiation of the apnea test. After that, mechanical ventilation was disconnected and an insufflation catheter was placed through the endotracheal tube at the level of carina to deliver 100% oxygen at 6.0 L/min. Arterial blood gas analysis (ABGA) was performed after approximately 8 to 10 minutes. If there was no respiratory drive or motion during the apnea test accompanied by the elevated level of $Paco_2$ >60.0 mm Hg, we confirmed the completion of the apnea test [8].

Study Design

In the current analysis, the patients were classified into 2 groups: the success group, in which the apnea test was completed, and the failure group, in which the apnea test was not completed. According to American Academy of Neurology guideline, the apnea test was immediately terminated and the case was defined as a failure of apnea test if it had any 1 of the following findings: severe hypoxemia (oxygen saturation by pulse oximeter <85%) for more than 30 seconds, development of critical cardiac arrhythmia, or sustained hypotension (systolic blood pressure [SBP] <90.0 mm Hg) despite appropriate fluid therapy and administration of vasopressors. For these cases, transcranial Doppler ultrasonography was used as an ancillary test to replace the apnea test [8]. Age, sex, cause of brain death, use of vasopressors, ABGA values, systolic and diastolic blood pressure (DBP) just prior to apnea test, mean arterial pressure, and central venous pressure were collected and compared between the 2 groups. The alveolar-arterial gradient (A-a gradient) and Pao_2/fraction of inspired oxygen [Fio_2] ratio were calculated to evaluate the respiratory status and lung function of each case. The standard A-a gradient formula was used, as suggested in the Mellemgaard study [9]:

$$\text{A} - \text{a gradient} = \text{PAO}_2 - \text{PAO}_2$$

$$\text{PAO}_2 = (\text{FIO}_2 \times [\text{P}_{\text{atm}} - \text{PH}_2\text{O}]) - (\text{PaCO}_2/0.8)$$

where P_{AO_2} is alveolar oxygen partial pressure, P_{atm} is defined as atmospheric pressure (760.0 mm Hg), P_{H_2O} is defined as water partial pressure (47.0 mm Hg at 37°C), Pao_2 is arterial oxygen partial pressure, and $Paco_2$ is arterial carbon dioxide partial pressure.

Statistical Analysis

Statistical analysis was performed using the Fisher exact test for categorical variables, and continuous variables were analyzed using the *t* test and expressed as mean (SD). Taking into account the results of the univariate analyses, the variables with $P < .05$ were included in the multivariate analyses performed by logistic regression, and the collinearity among the variables used in the linear regression was assessed to reduce the correlation between variables. Odds ratio (OR) along with 95% CI were reported, and receiver operating characteristic curve analysis assessed the cutoff value of significant risk factors associated with apnea test failure to prepare detailed guidelines for preapnea management. SPSS for Windows version 21.0 (IBM, Armonk, NY, United States) was used for statistical analysis. A P value $< .05$ was considered statistically significant.

RESULTS

During the study period, the apnea test was conducted on 527 patients, and 512 patients were analyzed after implementation of exclusion criteria. Fifteen patients died and did not undergo the apnea test: 6 patients showed refractory hypotension despite hemodynamic support, 5 patients died of lethal arrhythmia after cardiopulmonary resuscitation, 2 patients showed refractory metabolic acidosis, 1 patient had myocardial infarction during donor management, and 1 patient showed multiorgan failure after admission. Of the study population, the mean age was 48 (SD, 13) years (range, 17–74 years), and 340 patients (66.4%) were male. The apnea test was completed in 484 of 512 patients (94.5%), although the apnea test was aborted or failed in 28 patients (5.5%) because of progressive condition that developed shortly after disconnecting the mechanical ventilator, making a clinical diagnosis of brain death impossible. Regarding the causes of aborted apnea tests, 17 of them were caused by progressive hypotension and subsequent hemodynamic instability; in the remaining 11 patients, the test failed because severe refractory hypoxemia

occurred after sustained oxygen saturation by pulse oximeter <85%. The mean number of organs transplanted per single donor was 3 (SD, 1.3).

Table 1 demonstrates the comparative analysis of clinical and demographic characteristics between the 2 groups according to the success or failure of apnea test. In the current study, the leading cause of brain death was subarachnoid hemorrhage in both groups (121 patients, 26.2% in the success group vs 10 patients, 35.7% in the failure group), and there was no significant difference in mean age, sex, cause of death, or body temperature between the 2 groups.

Table 2 presents comparative analysis of pretest data and post-test outcomes between the groups according to the success or failure of the apnea test and in terms of hemodynamics; both the mean SBP and DBP measured before an apnea test were higher in the success group, whereas there was no significant difference in catecholamine use between the 2 groups. For the respiratory status on the basis of ABGA values, the mean values of pH and the Pa_{O_2} were greater in the success group than the failure group. The mean Pa_{O_2}/F_{IO_2} ratio was significantly higher, whereas the mean A-a gradient was lower in the success group. Among 512 patients who completed the apnea test, cardiopulmonary resuscitation was performed in 5 patients because of lethal cardiac arrhythmia.

The value of preapnea SBP, DBP, pH, Pa_{O_2}, A-a gradient, and P_{AO_2}/F_{IO_2} ratio were included in the multiple regression analysis (Table 3A), and the low SBP (OR, 0.976, 95% CI, 0.958–0.994; $P = .01$), low pH (OR, 0.004; 95% CI, 0.000–0.184; $P = .005$), and elevated A-a gradient (OR, 1.005; 95% CI, 1.003–1.008; $P = .001$) were found to be significant risk factors associated with apnea test failure. We examined the sensitivity and specificity of various cutoff values of SBP, pH, and A-a gradient for predicting failure of the apnea test using the receiver operating characteristic curve analysis as shown in Fig 1. The area under the curve (AUC) for the value of SBP was 0.705, and the optimal cutoff point to predict the apnea test failure was not more than 105.0 mm Hg (57.1% of sensitivity and 81.4% of specificity). The AUC for the value of the pH was 0.808, and the optimal cutoff value to predict the test failure was not more than 7.326 (82.1% of sensitivity and 75.4% of specificity). For respiratory status, the AUC of the value of A-a gradient was 0.805, and the optimal cutoff value of the A-a gradient was >556.4 mm Hg (sensitivity was 71.4% and specificity of 86.1%). The ORs for predicting apnea test failure were calculated based on the cutoff value for each risk factor and showed statistically significant OR of 3.433 for SBP not more than 105.0 mm Hg (95% CI, 1.412–8.348; $P = .007$), 8.082 for the pH not more than 7.326 (95% CI, 2.855–22.879; $P < .001$), and 8.737 for the A-a gradient more than 556.4 (95% CI, 3.495–21.839; $P < .001$) (Table 3B).

DISCUSSION

Confirmation of the absence of respiratory drive is one of the major diagnostic criteria for brain death. The successful completion of the apnea test could be one of the most effective ways to increase organ procurement rate by focusing on identifying appropriate management of risk factors associated with the apnea test failure. Our institution has managed a large number of potential brain death donors and served as a tertiary single center in the Republic of Korea. The authors conducted the assessment for risk factors of apnea test failure in a previously published study based on our database[10], which presented low SBP and high A-a gradient as the significant risk factors for apnea test failure.

Brain death is related to complex physiological alterations that lead to diffuse vascular regulatory disturbance with widespread cellular injury and commonly manifests in severe alterations in metabolism, immunology, coagulopathy, and endocrine function. This disturbance could lead to

Table 1. Comparative Analysis of Clinical Characteristics and Demographics Between 2 Groups; Success vs Failure of Apnea Test

Characteristics	Total (n = 512)	Success Group (n = 484)	Failure Group (n = 28)	*P* Value
Age, mean (SD), y	48 (13)	48 (13)	46 (16)	.45
Sex, No., M/F	340/172	324/160	16/12	.31
Etiology, No. (%)				.31
Traumatic brain injury	126 (24.6)	121 (25.2)	5 (17.9)	
ICH or IVH	90 (17.6)	84 (17.5)	6 (21.4)	
SAH	136 (26.6)	126 (26.2)	10 (35.7)	
Ischemic stroke	28 (5.5)	28 (5.8)	0 (0.0)	
Hypoxic brain damage	118 (23.0)	113 (23.3)	5 (17.9)	
Miscellaneous	14 (2.8)	12 (2.5)	2 (7.1)	
Use of vasopressor, No. (%)	502 (98)	474 (97.9)	28 (100)	>.99
Severity of ARDS, No. (%)				
Severe ARDS*	94 (18.4)	75 (15.5)	19 (67.9)	<.001
Moderate ARDS*	122 (23.8)	117 (24.2)	5 (17.9)	.65
Mild ARDS*	296 (57.8)	292 (60.3)	4 (14.3)	<.001

Abbreviations: ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; F, female; F_{IO_2}, fraction of inspired oxygen; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; M, male; PEEP, positive end-expiratory pressure; SAH, subarachnoid hemorrhage.

*The Berlin definition proposed 3 categories of ARDS based on degree of hypoxemia: mild (200 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O), moderate (100 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 200mm Hg with PEEP ≥ 5 cm H_2O), and severe (Pa_{O_2}/F_{IO_2} < 100 mm Hg).

Table 2. Comparative Analysis of Pre- and Post-Test Outcome Between 2 Groups; Success vs Failure of Apnea Test

Variable	Total (n = 512)	Success Group (n = 484)	Failure Group (n = 28)	*P* Value
Pretesting hemodynamic parameters				
Pretesting SBP, mean (SD), mm Hg	126.6 (25.2)	127.2 (24.5)	106.6 (30.0)	<.001
Pretesting DBP, mean (SD), mm Hg	76.9 (20.2)	77.6 (19.8)	64.4 (23.1)	.001
Pretesting MAP, mean (SD), mm Hg	93.3 (20.6)	94.1 (20.0)	78.4 (24.0)	<.001
Pretesting CVP, median (IQR), mm Hg*	6.0 (3.0–9.0)	6.0 (3.0–9.0)	8.0 (6.0–11.5)	.07
Body temperature, mean (SD), °C†	36.6 (0.9)	36.6 (0.9)	36.6 (1.00)	.85
Pretesting respiratory measurements				
pH, mean (SD)	7.372 (0.9)	7.378 (0.1)	7.27 (0.1)	<.001
Pa_{O_2}, mean (SD), mm Hg	177.3 (113.2)	181.7 (113.6)	101.0 (70.7)	<.001
Pa_{CO_2}, median (IQR), mm Hg*	36.0 (32.8–38.6)	36.0 (32.8–38.4)	42.3 (34.5–49.4)	.12
Pa_{O_2}/F_{IO_2}, mean (SD)	304.0 (248.2)	314.2 (250.1)	128.7 (116.3)	<.001
A-a gradient, mean (SD)	288.8 (221.7)	275 (217.6)	510.9 (167.7)	<.001
No. of donated organs, mean (SD)	3 (1.3)	3 (1.3)	2 (1.2)	.001
CPR because of arrhythmia, No. (%)	5 (1.0)	4 (0.8)	1 (3.6)	>.99

Abbreviations: A-a gradient, alveolar-arterial gradient; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; DBP, diastolic blood pressure; IQR, interquartile range; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; Pa_{O_2}, arterial partial pressure of oxygen; PaO_2/F_{IO_2}, arterial partial pressure of oxygen/fraction of inspired oxygen; SBP, systolic blood pressure.
*Data were compared using Mann-Whitney test when values did not show normal distribution. 25%-75% IQR.
†Body temperature was measured by tympanic thermometer.

multiorgan failure and even cause cardiovascular events in up to 60% of patients if not properly managed [11]. In the current study, we found that the elevated A-a gradient, low SBP, and acidemia before the apnea test were significantly associated with apnea test failure in the multivariate analysis.

First, the A-a gradient is identified as the difference between alveolar and arterial oxygen concentration, and an elevated A-a gradient would suggest hypoxia due to ventilation-perfusion mismatch or right-to-left shunting [10,12]. In an effort to prevent hypoxia-induced complications, the preoxygenation is usually performed for 10 minutes before the apnea test. Adequate preoxygenation eliminates the respiratory nitrogen and facilitates the oxygen transportation, whereas the inadequate oxygenation that causes the elevation of the A-a gradient would develop into hypotension or cardiac arrhythmia during the test. Besides, the elevated A-a gradient would reflect hypoxia as a result of acute lung injury (ALI). An elevated hydrostatic pressure across the pulmonary capillary membrane and uncontrolled sympathetic activity promote neurogenic pulmonary edema that leads to the ALI, and it causes inadequate oxygenation incurring the elevated A-a gradient [13].

Table 3. Risk Factors and the Cutoff Values of Failed Apnea Test

(A) Risk Factors Associated With Failed Apnea Test

Variable	Odds Ratio	95% CI	*P* Value
SBP, mm Hg	0.976	0.958–0.994	.01
pH	0.004	0.000–0.184	.005
A-a gradient, mm Hg	1.005	1.003–1.008	<.001

(B) Odds Ratios of Risk Factors of Failed Apnea Test According to the Cutoff Values

Variable	Odds Ratio	95% CI	*P* Value
SBP ≤105	3.433	1.412–8.348	.007
pH ≤7.326	8.082	2.855–22.879	<.001
A-a gradient >556.4	8.737	3.495–21.839	<.001

Abbreviations: A-a gradient, alveolar-arterial gradient; SBP, systolic blood pressure.

In addition, the level of Pa_{O_2} could affect the apnea test failure, and Pa_{O_2}/F_{IO_2} ratio is useful for estimating the degree of gas exchange and the severity of ALI. Although Pa_{O_2} and the Pa_{O_2}/F_{IO_2} ratio were not found to be significant risk factors in the multivariate analysis, they were significantly higher in the success group in univariate analysis. Moreover, the proportion of patients with severe acute respiratory distress syndrome was significantly higher in the failure group. Optimizing oxygen delivery would be important for preventing metabolic deterioration, and it contributes to preserving organ function [1,14] The respiratory function could be damaged by several factors during donor management, and the apnea test contributes to atelectasis and reduction in Pa_{O_2}/F_{IO_2} ratio [14].

For the potential donors with high A-a gradient or reduced Pa_{O_2}/F_{IO_2} ratio, aggressive management, such as frequent endobronchial suctioning, appropriate fluid resuscitation, or recruitment maneuver, would be necessary to prevent further lung injury or collapse [13]. Paries et al [14] reported that the apnea test induced a reduction of Pa_{O_2}/F_{IO_2} ratio, and a recruitment maneuver just after finishing the test could reverse these changes and prevent the loss of potential lung donors.

Regarding the hemodynamic aspects, when the ischemia of brainstem reaches the medulla oblongata, the transient autonomic storm with catecholamine surge causes the vasoconstriction and decrease of end-organ perfusion. After that, the catecholamine insufficiency leads to vasodilatation, decreased cardiac output, or hemodynamic instability. These changes could result in necrosis of the myocardium as a cause of cardiac arrhythmias [13]. In our results, the pretesting lower SBP was a significant risk factor for the apnea test failure, and we found high OR of 3.433 for

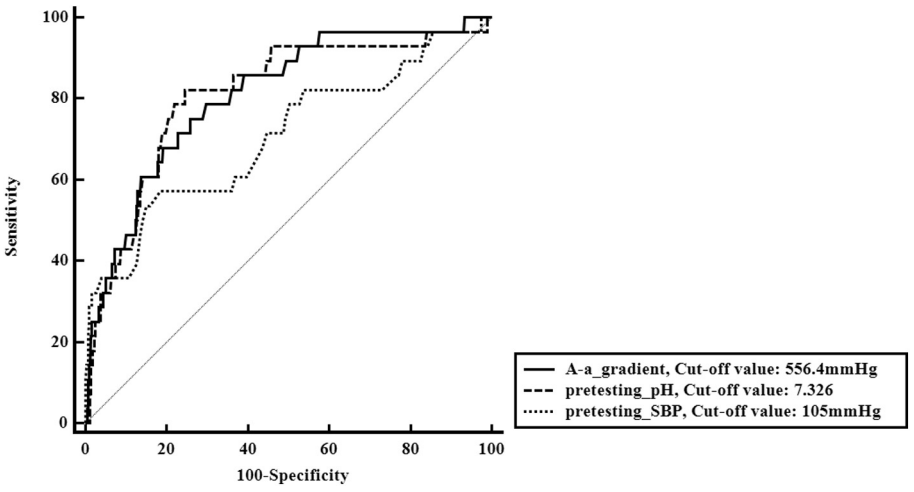

Fig 1. Receiver operating characteristic curve analysis establishing the cutoff value of systolic blood pressure, pH, and A-a gradient to predict the apnea test failure. ROC, receiver operating characteristic; SBP, systolic blood pressure.

pretesting SBP not more than 105.0 mm Hg in the multivariate analysis. Correcting cardiovascular disturbance would be necessary to optimize end-organ perfusion for graft function and consequently prevent apnea test failure. To do this, the authors suppose that the restoration of euvolemia is the first step by administration of intravenous fluid, and pharmacologic therapy should be promptly conducted, such as catecholamine or vasoconstrictors, if the hemodynamic stabilization is not accomplished despite fluid resuscitation [1,13]

In addition, our results demonstrated that the pretesting acidemia was the predisposing factor for a failed apnea test, and pH not more than 7.326 had a significantly high OR of 8.082. During the apnea test, CO_2 could not be released from blood to alveoli; then the respiratory acidosis began to develop and the acidemia caused the reduction in peripheral arterial resistance or contractile force of ventricle. As the result, these cardiovascular depressions could exceed the sympathetic response associated with cardiovascular stimulation. Kramer et al [5] asserted that serial ABGA at fixed intervals should be performed, and the apnea test should be finished immediately when the diagnostic criteria for brain death are achieved to avoid hemodynamic complications related to severe respiratory acidosis. Kim et al [6] also observed that end-tidal CO_2 monitoring during the apnea test reduces the test duration and would be instrumental in hemodynamic stabilization. An appropriate correction of acidemia before the test would increase the success rate of apnea test and improve the hemodynamics, especially in cases of the pretesting pH not more than 7.326.

Our study proposed the cutoff value of significant risk factors for failed apnea tests. Deriving cutoff values that could represent physiological status has important implications because the current aim of brain dead donor management would move from traditional graft survival to specific physiological goal-directed targets, such as hemodynamics or oxygenation status [15]. Our results found the cutoff values of pretesting SBP not more than 105.0 mm Hg, pretesting pH not more than 7.326, and pretesting A-a gradient more than 556.4 mm Hg adequate to enable targeted therapy for donor management. In fact, the optimal management of potential organ donors has been overlooked in transplantation in spite of its clinical importance. Because the potential organ donor might have profound physiological and homeostatic changes as described above, the successful donation and satisfactory graft outcomes could depend on the preserved hemodynamic stability in the potential donor [13]. Authors expect that these cutoff values could provide a guide as the critical care endpoints of donor management goals for better transplant outcome. Regarding the expanded donor pool, expanded criteria donors (ECDs) have been more commonly used as the source of organs for transplant, and this current study also includes ECDs, which accounts for the total number of 35% of enrolled donors. The ECDs are usually older than standard criteria donors with more severe comorbidities, and there should be a growing emphasis on the importance of intensivists' role to optimize donation potential in patients with brain death [15,16] Determination of cutoff value of risk factors could help the intensivists redeem the disadvantages of ECDs by means of appropriate donor management.

To our knowledge, this is the first study analyzing the cutoff value of risk factors associated with the apnea test failure. Despite these interesting results, our research has limitations inherent to the retrospective design of the study. It was difficult to implement the uniform treatment to a standardized protocol for stressful conditions, such as hypotension or hypoxia, and it could not be ruled out that decisions for management might be changed according to various clinical situations. However, the authors expect that these limitations could be reduced by performing donor management by a single intensivist under the consistent management strategy that provides the uniformity of donor management based on survival sepsis campaign and strict lung protective mechanical ventilation. Although the sample

size was relatively larger than our previous study, statistical power was lacking to derive more precise cutoff values. Therefore, we suppose that a large-scale prospective study is needed to confirm the current study results. Also, further studies are needed to identify how physiologically targeted management associated with risk factors of apnea test failure affects the long-term outcome of graft after transplant.

In conclusion, the pretesting low SBP of not more than 105.0 mm Hg, pretesting acidemia pH of not more than 7.326, and pretesting high A-a gradient more than 556.4 mm Hg were presented as significant predisposing factors for apnea test failure in potential brain dead donors. Considering the disparity between supply and demand of organs, early recognition and aggressive management for these risk factors is important to reduce failure rates of apnea test and consequently improve outcome of organ procurement.

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