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ORIGINAL ARTICLE

Predictors of Apnea Test Failure During Brain Death Determination

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Abstract
Background In a recent publication (Wijdicks et al. in Neurology 71(16):1240, 2008), apnea test safety during brain death determination was evaluated at a single tertiary care center. One major conclusion was that apnea testing was safe in hemodynamically compromised patients in most circumstances and rarely aborted. Determinants of apnea test completion failure are unknown.
Methods A–a gradients and $P_{a_{O_2}}/F_{i_{O_2}}$ ratios were calculated in the previously studied cohort. Arterial blood gas (ABG) values and systolic blood pressures (SBP) were recorded prior to apnea test initiation. Patients that completed the procedure during the declaration of brain death were compared to those whose studies were aborted. Statistical analysis was performed using Wilcoxon rank-sum and Fisher's exact tests where appropriate. Aborted apnea test risk factor assessment was by logistic regression analysis.
Results 207 of the original 228 patients were evaluated. 10 of the 207 patients had aborted apnea tests because of hypoxemia and/or hypotension. 60% who failed the apnea test were male and were of younger age [median: 23 years vs. median: 47 years ($P = 0.02$)]. A–a gradient median values for aborted and completed apnea tests were 376 and 175 mmHg, respectively ($P = 0.003$). Neither the $P_{a_{O_2}}/F_{i_{O_2}}$ ratio ($P = 0.14$) nor SBP ($P = 0.28$) were associated with test completion failure. Acidemia preceding a carbon dioxide challenge was independently associated with test completion failure ($P = 0.028$).
Conclusion Acute lung injury is common in patients undergoing brain death evaluation. Patients that failed completion of apnea testing tended to be younger, had significantly greater A–a gradients, and were more acidotic.

Keywords Acute lung injury · Apnea · Blood gas analysis · Brain death · Prognosis

Introduction

The oxygen-diffusion method of apnea testing is a technique commonly used in the evaluation of brain death [1, 2]. The safety of this procedure has been recently evaluated and only rarely had to be aborted [3]. Acute lung injury is common in critically ill brain-injured patients and after brain death, which often results from trauma, neurogenic pulmonary edema, or aspiration. Abnormal chest X-ray and respiratory measurement findings are typically reasons to pause before performing the apnea test. Adequate pre-test oxygenation removes alveolar nitrogenous stores and facilitates oxygen exchange [4]. We postulated that poor pretest pulmonary gas exchange would compromise a carbon dioxide challenge with direct oxygen flow close to the alveoli.

Patients and Methods

The A–a gradient and $P_{a_{O_2}}/F_{i_{O_2}}$ were calculated for patients in the previously studied cohort [3]. Arterial blood

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gas (ABG) values were obtained immediately preceding the start of apnea testing. Patients that completed the procedure during the declaration of brain death were compared to those whose studies were aborted. The standard A–a gradient formula [5] used was:

- A–a gradient = $P_{A_{O_2}} - P_{a_{O_2}}$
- $P_{A_{O_2}} = \left(F_{i_{O_2}} \times [P_{atm} - P_{H_2O}]\right) - \left(P_{a_{CO_2}} \div 0.8\right)$

$P_{A_{O_2}}$ represents alveolar oxygen partial pressure, $P_{a_{O_2}}$ represents arterial oxygen partial pressure, $P_{a_{CO_2}}$ represents arterial carbon dioxide partial pressure, and $F_{i_{O_2}}$ represents inspired oxygen fraction. P_{atm} represents the atmospheric pressure (760 mmHg) and P_{H_2O}, water partial pressure (47 mmHg at 37°C). Systolic blood pressure (SBP) preceding apnea testing was recorded.

Statistical analysis was performed using the Wilcoxon rank-sum tests for continuous variables due to non-Gaussian distribution of the data. Fisher's exact tests were used to compare categorical variables due to limited sample size for patients who aborted apnea test. Associations between the apnea test completion status and potential risk factors were assessed using univariate logistic regression. Odds ratios along with 95% confidence intervals were reported. All the tests were 2 sided and *p*-values less than 0.05 were considered statistically significant. Analysis was performed using SAS version 9.0 software (SAS Inc., Cary, NC, USA).

Results

The A–a gradient was calculated for 207 of the 228 patients with a brain death evaluation. Twenty patients from the original cohort did not undergo a carbon dioxide challenge: nine patients were unsafe for testing because of refractory hypotension despite hemodynamic support; nine patients had pulmonary compromise [refractory hypoxemia and positive end expiratory pressure requirements ≥ 15 cm H_2O; two patients had diffuse pulmonary edema (one with associated pneumothorax) and one diagnosed with pulmonary contusion]. Two additional patients were not tested for other reasons (e.g. cerebral silence on EEG before apnea testing attempted; barbiturate intoxication as confounder, nuclear scan performed as confirmatory study). One patient was excluded from the current analysis due to erroneous ABG values.

Apnea testing was aborted in 10 of the 207 patients because of progressive hypotension or hypoxemia that developed shortly after disconnecting ventilatory support. Table 1 summarizes the clinical characteristics and reasons for test failure. Sixty percent of those with apnea test failure were male versus 51% in the comparative group ($P = 0.75$). Younger patients were more likely to have aborted apnea tests (median age: 23 years, 25–75% quartile: 19–42 years) when compared to those who completed the procedure (median age: 47 years, 25–75% quartile: 25–62 years) ($P = 0.02$). Seventy percent of the patients in the aborted group died of complications related polytrauma versus only 25% in the comparative group.

A higher A–a gradient was associated with apnea test failure ($P = 0.003$). The median A–a gradient in this group was 376 mmHg (25–75% quartile: 255–476 mmHg) compared to 175 mmHg (25–75% quartile: 104–282 mmHg) in those who successfully completed apnea testing. Interestingly, the presence of acidemia just prior to initiation of a carbon dioxide challenge was independently associated with test completion failure ($P = 0.028$). The median

Table 1 Clinical characteristics of patients who failed the apnea test

Patient	Age/sex	A–a gradient	Pre-testing SBP	Reason for aborted study	Pre-apnea testing respiratory measurements			
					pH	$P_{a_{O_2}}$	$P_{a_{CO_2}}$	PF ratio
1	13/M	448	120	Hypotension/hypoxemia	7.44	85	30	106
2	17/F	278	140	Unclear[a]	7.28	393	34	393
3	19/M	561	161	Hypotension/hypoxemia	7.40	111	33	111
4	19/M	570	100	Hypoxemia	7.45	87	35	87
5	20/F	184	94	Hypotension/hypoxemia	7.30	186	39	258
6	26/M	426	110	Hypotension/hypoxemia	7.27	242	36	242
7	36/F	324	100	Hypoxemia	7.24	270	39	236
8	42/M	80	65	Hypotension/hypoxemia	7.36	163	34	408
9	42/M	431	100	Hypoxemia	7.20	74	52	74
10	55/F	325	100	Hypotension/hypoxemia	7.16	420	41	338

Age determined in years

A–a, gradient alveolar–arterial oxygenation gradient; SBP, systolic blood pressure (mm Hg); PF ratio, partial pressure of arterial oxygenation/fraction of inspired oxygen; $P_{a_{O_2}}$, partial pressure of arterial oxygenation (torr); $P_{a_{CO_2}}$, partial pressure of arterial carbon dioxide (torr)

[a] Patient 2 apnea test was aborted for unclear reasons (e.g. no documented hypotension/hypoxemia during procedure)

values of those who had aborted procedures was 7.29 (25–75% quartile: 7.23–7.41) versus 7.39 (25–75% quartile: 7.33–7.44) in the comparative group. However, neither the P_{aO_2}/F_{iO_2} ratio ($P = 0.14$) nor other independent ABG measurements (e.g., pre-P_{aCO_2} or pre-P_{aO_2}) yielded similar associative power. Pre-test SBP (P value $= 0.28$) also did not correlate with apnea test failure. Table 2 summarizes these findings in addition to brain death etiology. Age, pre-test pH, and A–a gradient were associated with test completion failure after logistic regression analysis.

Discussion

Documentation of absent respiratory drive fulfills one major diagnostic criterion for the clinical determination of brain death [1, 2]. Safety concerns (e.g. hypotension, pneumothorax, cardiac dysrhythmia) while performing the apnea test were recently assessed, and the apnea test was found to be safe in most circumstances [3]. However, risk factors such as inadequate pre-test oxygenation may lead to complications [4]. In this study, we found that age, acidemia at the time of starting the apnea test, and an elevated A–a gradient are associated with inability to complete the apnea test.

The A–a gradient helps differentiate intra versus extra-pulmonary causes of poor oxygenation by measuring differences between alveolar and arterial oxygen concentration. This calculation also accounts for changes in respiration as measured by P_{aCO_2}. Abnormally elevated gradients suggest a defect in gas exchange (e.g. ventilation/perfusion mismatch, right to left shunting). A previous

Table 2 Risk factors associated with apnea test failure and cause of death

Variable	Apnea test			
	Completed ($n = 197$)	Aborted ($n = 10$)	OR (95% CI)	P value
Demographics				
Age (median) (25–75% quartile)	47 (25–62)	23 (19–42)	0.97 (0.52, 0.98)[§]	0.02*
Gender				
Male (No of patients)	101	6	1.41 (0.39, 5.16)	0.75
Female (No of patients)	96	4	Reference	
Respiratory measurements (median) (25–75% quartile)				
A–a gradient	175 (104–282)	376 (255–476)	1.01 (1.03, 1.13)[§]	0.003*
PF ratio	280 (195–376)	239 (101–352)	1.0 (0.99, 1.001)	0.14
Pre-apnea test arterial blood gas:				
pH	7.39 (7.33–7.39)	7.29 (7.23–7.41)	<0.001 (<0.001, 0.13)	0.028*
P_{aCO_2}	40 (36–43)	36 (34–40)	0.93 (0.83,1.04)	0.12
P_{aO_2}	249 (139–382)	175 (87–301)	1.0 (0.99, 1.002)	0.16
Hemodynamic measurements				
SBP (median) (25–75% quartile)	110 (100–124)	100 (99–125)	0.98 (0.95, 1.02)	0.28
Vasopressor use (# of patients)	197	10		
Etiology of brain death				
Traumatic brain injury	51	7		
Intracranial hemorrhage	50	1		
Subarachnoid hemorrhage	39	1		
Ischemic stroke	17	1		
Anoxic injury	20	0		
Miscellaneous	21	0		

Age, measured in years

A–a gradient, alveolar–arterial oxygen gradient measured in millimeters of mercury; PF ratio, partial pressure of arterial oxygen/fraction of inspired oxygen; P_{aCO_2}, partial pressure of arterial carbon dioxide (torr); P_{aO_2}, partial pressure of arterial oxygenation (torr); SBP, systolic blood pressure measured in millimeters of mercury (SBP readings were not available in 11 patients); Intracranial hemorrhage, includes intraparenchymal, cerebellar, brainstem or pontine, subdural, intraventricular; Ischemic stroke, includes cerebral, cerebellar, brainstem or pontine; Miscellaneous, includes brain tumor, central nervous system infection, brain edema and fulminant hepatic failure, acute hydrocephalus, and battering

[§] Odds ratio and 95% CI are reported for 10 unit increments

* P values < 0.05 were considered significant

study did not demonstrate the increased risk of complications from an elevated gradient preceding the apnea test, but it analyzed a smaller sample of patients [4]. The P_{aO_2}/F_{iO_2} ratio is useful at estimating severity of gas exchange at higher F_{iO_2} levels. While the P_{aO_2}/F_{iO_2} ratio was not associated with apnea test failure in our analysis, it did demonstrate that neurologically devastated individuals undergoing brain death evaluation often have coexisting diffuse lung injury. Furthermore, we found that A–a gradients were two-fold higher in those who failed the apnea test, which was significant after logistic regression. These findings suggest that although most patients undergoing brain death evaluation have variable degrees of acute lung injury, the presence of greater intrapulmonary oxygen shunting and poorer ventilation (e.g., P_{aCO_2}), as defined by the A–a gradient, lead to poorer tolerability during a carbon dioxide challenge.

A striking finding was that despite normalization of pretest P_{aCO_2}, the presence of concomitant acidemia was associated with apnea test failure. The superimposed respiratory acidosis that develops during the procedure likely contributes significantly to hemodynamic compromise in those with underlying acidemia. Aborted apnea tests occurred more often in younger individuals. This counterintuitive association may be explained by selection bias; more aggressive testing may have been pursued in the younger population despite poorer clinical conditions (e.g. polytrauma), while greater caution may have been exercised when pursuing the apnea test in older patients.

Physicians performing a brain death examination should be aware that acidemia and markedly increased A–a gradients preceding apnea test may compromise successful testing. Still, the A–a gradient is increased in most patients with uncomplicated apnea tests, and we could not identify a cutoff value that precludes apnea testing.

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