Intensive Care Med (1995) 21:247–252

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Apnea testing in suspected brain dead children – physiological and mathematical modelling

Received: 12 November 1993
Accepted: 11 February 1994

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Abstract *Objective:* To study the validity and safety of the traditional apnea test in children, and to evaluate a mathematical equation estimating the hemodynamic response to the apnea test.
Design: A prospective clinical study.
Setting: Pediatric ICU.
Patients and participants: 38 pediatric patients suffering severe brain injury aged 2 months to 17 years, undergoing apnea testing for brain death.
Measurements and results: Apnea tests were performed 61 times (once in 19 patients, twice in 15, and 3 times in 4 patients). Mean $PaCO_2$ was 41.1 ± 10.6 mmHg before apnea and increased to 68.0 ± 17.6 at 5 min. $PaCO_2$ increased to 81.8 ± 20.1 and 86.0 ± 25.6 at 10 and 15 min, respectively. There was a mean $PaCO_2$ increase by 5.38 ± 1.4 mmHg/min in the first 5 min, and 2.75 ± 0.5 mmHg/min during the next 5 min. We found a statistically significant ($p < 0.05$) linear relationship between the natural logarithm of $PaCO_2$, time, and the logarithm of the initial level of $PaCO_2$. An inverse linear relationship ($p < 0.05$) was found between systemic mean arterial pressure (MAP) and initial level of $PaCO_2$ presented as mathematical correlations and nomograms.
Conclusions: By using our model for predicting MAP and PCO_2 prior to apnea testing, hemodynamic embarrassment can be anticipated and prevented, thus allowing a safer procedure in the detection of brain death. Despite the fact that continuous cardiorespiratory monitoring is important, hemodynamic disturbances can be estimated before the apnea test, thus allowing a safer approach to brain death detection.

Key words Apnea test · Brain death · Hypercapnia

Introduction

Medical and technological advances introduced over the past three decades have resulted in a total revision of the old concept linking death to the cessation of cardiac and respiratory functions. Brain death is now accepted both medically and legally as synonymous with death in the United States and in most European countries [1]. The diagnosis of brain death requires irreversible cessation of cortical and brain stem function, including apnea. In order to confirm apnea, the $PaCO_2$ level must be high enough to provide stimulation of the medullary respiratory center [2]. Methods of apnea testing and the duration of apnea required to declare brain death vary. These range from simple observation of the patient, while off-ventilatory support, to rigorous "oxygenated" apnea testing with measurements of $PaCO_2$ [3]. In normal children, the acute depressive cardiovascular effect of acute hypercapnia are counteracted by the increased sympathetic tone, resulting in increased blood pressure, heart rate and cardiac index. However, in brain death, when the sympa-

thetic response is impaired, acute hypercapnia may induce circulatory depression. Previous studies reported no significant hypoxemia or hemodynamic compromise during apnea testing, or have not been specific in the description of these complications [2, 4, 5].

We report our experience with the apnea test for the diagnosis of brain death in the pediatric age group. This prospective protocol was designed: i) to assess the validity of the traditional apnea test in children; ii) to study the safety and feasibility of apnea testing in children in whom brain death is suspected; iii) to evaluate a mathematical equation estimating the hemodynamic response to the apnea test.

Materials and methods

We prospectively studied apneic oxygenation in 38 patients aged 2 months to 17 years (mean 4.7 years) undergoing apnea testing for brain death. All patients were in deep, unresponsive coma, with absent brain stem reflexes. The cause of death was established in every patient. None were hypotensive, hypothermic, sedated, or paralyzed, and all maintained brain death criteria throughout the observation and testing periods. Principal diagnoses were: head trauma in 29 patients; hypoxic encephalopathy in 2 patients; intracranial infection in 2; brain tumors in 2; intracranial hemorrhage in 2; and acute hydrocephalus secondary to blocked ventriculo-peritoneal shunt in one patient.

Apnea tests were performed 61 times (once in 19 patients, twice in 15 patients, and 3 times in 4 patients) as follows: patients were preoxygenated with 100% oxygen for ten minutes before disconnection from the ventilator. Subsequently, a continuous flow of oxygen at 3–6 l/min was provided via a catheter in the endotracheal tube. Arterial blood gases were obtained at 0, 5, 10, 15 min of apnea through indwelling arterial lines. Temperature, pulse rate, and blood pressure were observed continuously, as were respiratory efforts. Ventilation was resumed if spontaneous respiration or cardiovascular instability ensued (defined as a >10% change from the baseline value of either blood pressure or heart rate) [4].

Variance component analysis (unbalanced ANOVA with repeated measures) was used for statistical analysis [6]. This is the standard statistical method designed for examining data with repeated measures, including models where each subject is observed for a different number of times. This methodology permits evaluation of more variables (apnea tests), thus increasing the statistical power of the analysis [6].

Results

Of the 61 apnea tests, only one patient showed spontaneous respiratory movements during apnea testing. Spontaneous respiratory movements occurred 3.5 min after disconnection at a $PaCO_2$ of 49 mmHg, indicating the presence of residual brain stem function. When retested within 24 h, this patient had no respiratory movements.

Hemodynamic instability was observed in 8 apnea tests. In 7 patients, significant hemodynamic depression occurred three to 12 min after disconnection. One patient developed cardiac arrest 15 s after being disconnected from the ventilator. This patient was receiving inotropic support and was hemodynamically unstable, so the role of the apnea test was not clear. This was a 3-year-old child who suffered severe closed head injury. His examination met criteria for brain death 24 h after admission. Despite vigorous fluid and blood resuscitation, he remained hemodynamically unstable and required inotropic support with dopamine and epinephrine. However, despite ongoing support and adequate ventilation the patient developed metabolic acidosis and required large and frequent infusions of sodium bicarbonate. Prior to the apnea test he was ventilated by a mechanical ventilator (Servo 900C, Siemens) with ventilatory settings of 15 breaths/min, a peak inspiratory pressure of 28 cmH_2O, and a FIO_2 of 0.6. An arterial blood gas prior to apnea testing showed pH of 7.27, PCO_2 of 35 mmHg, PO_2 of 182 mmHg, and bicarbonate 17 mmol/l.

Due to his unexpected cardiac arrest, a repeat test was not done. In the 2 other tests which failed to reach a $PaCO_2$ of 60 mmHg because of hemodynamic instability, tests were repeated. No respiratory movement occurred in either test after disconnection, and the $PaCO_2$ exceeded 60 mmHg without hemodynamic instability.

In the other 5 patients with hemodynamic instability, $PaCO_2$ was over 60 mmHg before ventilation was resumed, confirming the diagnosis of brain death when apnea test was concluded.

Arterial $PaCO_2$ increased most rapidly during the initial 5 min of apnea (5.38 ± 1.41 mmHg/min). The increment was 2.75 ± 0.5 and 1.01 ± 1.08 during the following second and third 5-min periods, respectively. The average rate of $PaCO_2$ increase was 3.04 ± 1.00 mmHg/min.

Mean $PaCO_2$ was 41.18 ± 10.6 mmHg before apnea, and 68.07 ± 17.66 at 5 min. $PaCO_2$ was 81.8 ± 20.2 mmHg, and 86.88 ± 25.6 at 10 and 15 min, respectively (Table 1, Fig. 1).

After 5 min of apnea, $PaCO_2$ was still below 60 mmHg in 16/60 tests (26.7%). Initial PCO_2 in 11/16 tests was below 40 mmHg, and in the other 5/16, below 30 mmHg. However, in only 3 of 41 (7.3%) apnea tests

Table 1 Serial arterial PCO_2 levels during apnea testing

Time (min)	$PaCO_2$[a] (mmHg)	$PaCO_2$ change (mmHg/min)
0	41.18 ± 10.6	
0–5 min		5.38 ± 1.41
5	68.07 ± 17.66	
5–10 min		2.75 ± 0.50
10	81.81 ± 20.2	
10–15 min		1.01 ± 1.08
15	86.88 ± 25.6	

[a] All values are mean ± SEM

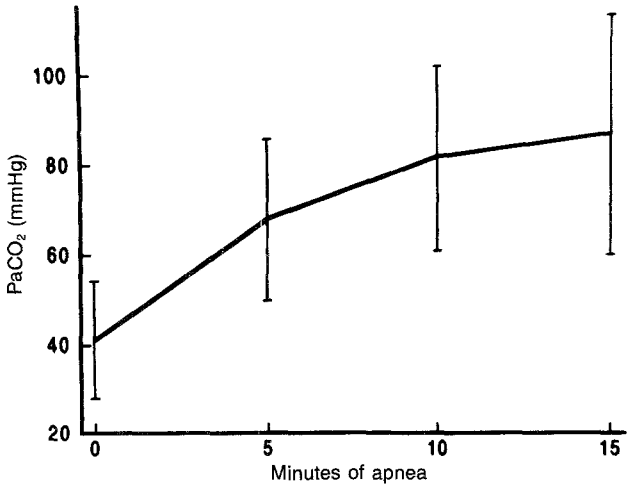

Fig. 1 Mean values for serial arterial blood gases and pH at baseline and during apnea test in patients with suspected brain death. See text for details. $PaCO_2$ indicates partial arterial carbon dioxide pressure

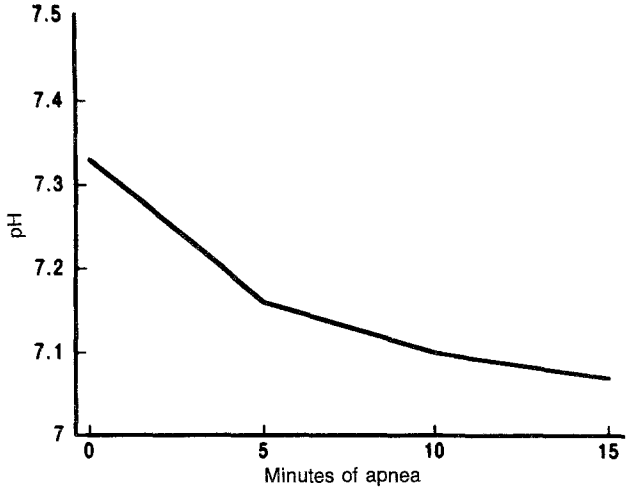

Fig. 3 Mean values for arterial pH at baseline and during apnea test in patients with suspected brain death. See text for details

lasting 10 min, PCO_2 did not reach the critical level of 60 mmHg. In all three initial PCO_2 was below 30 mmHg.

Using variant component analysis, a direct linear relationship was found between the natural logarithm of $PaCO_2$, time, and the natural logarithm of $PaCO_2$ at the beginning of the test:

$$\text{Ln } PaCO_2 = 0.69 + 0.072 + 0.86 \text{ Ln } PaCO_2O$$

($p < 0.05$) (Fig. 2), where Ln = natural logarithm; $PaCO_2O = PaCO_2$ at the beginning of test; t = time in min.

There was no relationship between the rate of increase of $PaCO_2$ and initial PaO_2 at the beginning of the test.

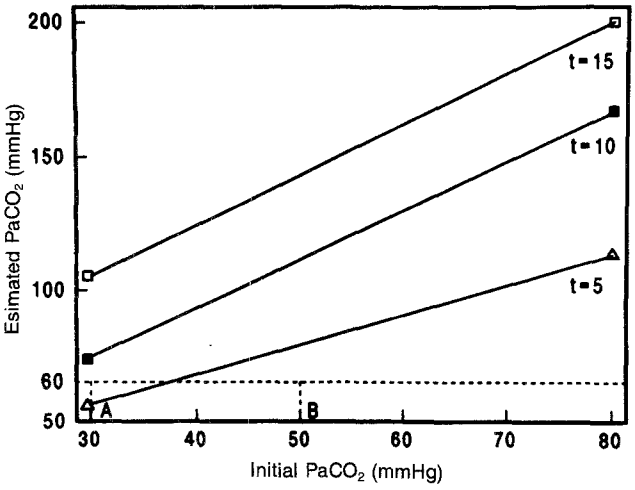

Fig. 2 Graph showing estimated PCO_2 at 5, 10, 15 min in relation to baseline PCO_2. *Triangles* represent PCO_2 at 5 min; *closed boxes* represent PCO_2 at 10 min; and *open boxes* represent PCO_2 at 15 min. To use the nomogram find the intercept of the patient's PCO_2O and time

Mean arterial pH was 7.33 ± 0.09 at onset, and decreased to 7.16 ± 0.08 at 5 min. Mean pH was 7.1 ± 0.08 and 7.07 ± 0.08 at 10 and 15 min, respectively (Fig. 3).

The average decrease in mean pH was 0.032 ± 0.0088/min during the first 5 min, and -0.018 ± 0.015 during the following 5 min. Arterial pH levels decreased below 7.1 in 9/60 tests within 5 min, and in 17/60 tests within 10 min. In 3/60 tests pH decreased below 7.0 within 10 min of apnea. In other tests pH did not decrease below 7.1.

All patients were well oxygenated prior to testing. Mean PaO_2 fell from 209.74 ± 121.82 mmHg to 182.78 ± 121.98 mmHg at 5 min, and to 183.45 ± 127.28 mmHg and 170.74 ± 114 mmHg at 10 and 15 min of apnea, respectively.

Variance component analysis produced the following equation for prediction of mean arterial blood pressure (MAP):

$$MAP = 78.22 - 1.7\,t - 0.33\,PaCO_2O + 0.038\,PaO_2O$$

($p < 0.05$) (Figs. 4, 5), where $PaO_2O = PaO_2$ at beginning of test. t = time in min.

No statistically significant correlation was found between MAP and pH 0 (pH at beginning of test), nor did we find a statistical significant model for predicting changes in PaO_2.

Discussion

The demonstration of apnea is one essential criterion for determination of brain death. Various studies have attempted to define adequate carbon dioxide tensions for stimulation of medullary respiration in severely brain damaged patients. $PaCO_2$ in the range of 44–60 mmHg has been suggested [2–5, 7]. We chose a value of

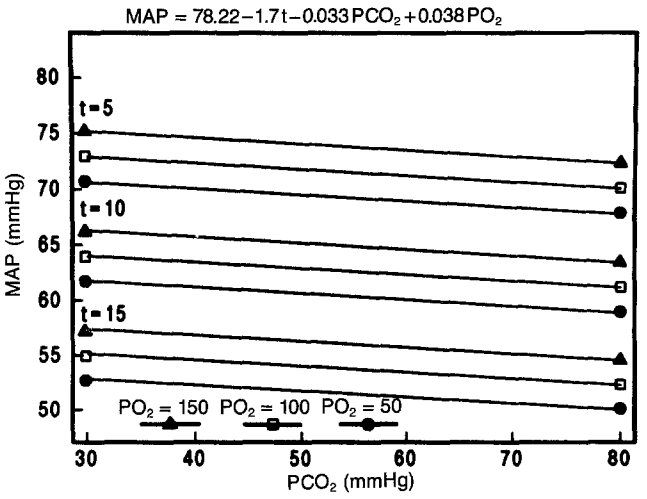

Fig. 4 Graph showing estimated mean arterial pressure (MAP) in relation to baseline PCO_2 at different levels of PO_2. *Triangles* represent PO_2 of 150 mmHg; *boxes* represent PO_2 of 100 mmHg; *circles* represent PO_2 of 50 mmHg

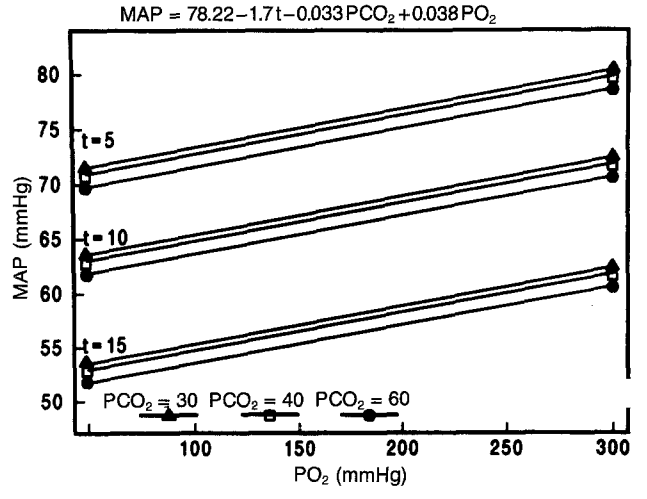

Fig. 5 Graph showing estimated mean arterial pressure (MAP) in relation to baseline PO_2 at different levels of PCO_2. *Triangles* represent PCO_2 of 30 mmHg; *boxes* represent PCO_2 of 40 mmHg; *circles* represent PCO_2 of 60 mmHg

60 mmHg, as suggested by the President's Commission report [8] and advocated by others [4, 7, 9, 10].

There are several methods to deliver oxygen during the apnea test; a catheter placed within the endotracheal tube, a T-piece attached to the endotracheal tube, and positive end expiratory pressure at a level of 4–5 cmH_2O, using an intermittent mandatory ventilatory circuit [4, 11, 12]. A theoretical problem with oxygenation by cannula is carbon dioxide washout, decreasing the rate of $PaCO_2$ rise. However, it has been shown that flow rates of 3–6 l/min eliminate carbon dioxide washout almost entirely [12]. Our patients were well oxygenated, using 100% oxygen at their pretesting respirator rate/volume settings for ten minutes before discontinuing ventilation. Oxygen was then delivered at 3–6 l/min through a tracheal catheter.

The duration of apnea suggested in order to confirm brain death has varied from 3–20 min [2, 9, 10, 13]. Eger and Severinghaus [13] found that the rate of rise of $PaCO_2$ in normal anesthetized adults was 13.4 mmHg/min during the first min, with a subsequent linear rate of 4.2 mmHg/min during periods of 4–11 min. They attributed this change in rate to an early equilibration of alveolar PCO_2 with venous blood during the first 15–45 s. The initial rise was equal to the arteriovenous difference for PCO_2, and the subsequent slower rise was thought to represent the balance between metabolic production of carbon dioxide and the available carbon dioxide storage capacity of the body. Rowland [9] found that the average increase in $PaCO_2$ in normocapneic or hypocapneic children with suspected brain death was 4.2–4.4 mmHg/min during the first 5 min, and 3.4 mmHg/min during the next 5 min of apnea. Outwater et al. found an average of 4.4 mmHg/min increase during the first 5 min of apnea after evaluating ten children who were brain dead [10]. They recommended an initial test of 5 min duration before reinstituting mechanical ventilation. Our study confirms that the rate of rise of $PaCO_2$ after onset of apnea follows a similar course: the initial rate of rise was rapid, followed by a slower rate later on. In our study $PaCO_2$ increased 5.38±141 mmHg/min during the first 5 min, and 2.75±0.5 mmHg/min during the next 5 min. In adult brain dead patients, Shaffer, Ropper and Pitts [2, 4, 5] reported arterial $PaCO_2$ increments of 2.4, 3.2, and 2.4 mmHg/min, respectively.

Mean PCO_2 increase during apnea was lower in our patients than has previously been reported in anesthetized patients who were not brain-dead [15]. This may have resulted from the loss of CO_2 production by the brain and from loss of spontaneous movements associated with brain death, which also diminishes CO_2 production [4]. However, the increase is higher than that described in adults, and is probably secondary to the increased metabolic rate in children [10].

The formula and graph (Fig. 2) for predicting $PaCO_2$ is suggested as a quick reference for assessment of the time required to reach the desired PCO_2. To use the nomogram: Find the intercept of the patient's initial $PaCO_2O$ and desired $PaCO_2$ It is seen from the curves that more than 5 min are required to reach a PCO_2 of 60 mmHg when $PaCO_2O$ is 30 (point A), while only less than 5 min are required to reach a PCO_2 of 60 mmHg when $PaCO_2O$ is 50 (part B). A limitation of our study imposed by the study design is that nomograms of MAP were done for all patients, regardless of age. However, this limitation is not significant, as the correlation between MAP, PaO_2 and $PaCO_2$ were not age-dependent.

Brain dead patients may manifest considerable cardiopulmonary instability [16]. The apnea test may result in detrimental hypoxemic cardiovascular compromise and hypercapnia. The circulatory response to hypercapnia is a balance between the peripheral and central effects of CO_2. Carbon dioxide depresses myocardial contractility and causes peripheral vasodilation. However, it may increase sympathetic tone by indirect action through the central nervous system. Pulse and blood pressure changes of 10% or greater during apnea test were used as indicators of hypoxia [4]. We have observed hemodynamic instability in 8/61 apnea tests. One patient with head injury developed cardiac arrest 15 s after being disconnected from ventilatory support without being hypercarbic or hypoxic. Resuscitation was unsuccessful, and direct cause of arrest remained undetermined. The arrest might have been related to the ongoing metabolic acidosis associated with diminished myocardial function, or to a reduction in blood flow secondary to a decrease in intrathoracic pressure [17].

Kissoon et al. described [16] asystolic events in 5 of 26 organ donors, and attributed these to loss of vasomotor tone, catecholamine release, or metabolic changes such as acidosis hypothermia or hyperkalemia. Hemodynamic instability may be related to lack of thyroid hormone [18], or to excessive catecholamine storm, as described by Grose et al. [19].

Riviello et al. [20] reviewed data related to hemodynamic changes occurring independently of hypoxemia during the apnea test. They concluded that pulse rate and blood pressure changes are not predictive of hypoxemia. Previous pediatric reports [9, 10] have noted isolated bradycardia in patients with arterial $PaO_2 < 80$ mmHg. Benzel et al. [13] observed no significant hemodynamic alterations in 20 adult brain dead patients during the apnea test despite the fact that 50% of this group had a premorbid underlying cardiac abnormality [21]. Other authors noted elevation in blood pressure after several minutes of apneic oxygenation [15, 22]. Wetzel et al. [23] described a hypertensive response to operative stimuli in brain dead organ donors, and suggested the existence of intact spinal reflex arcs between pain and sympathetically mediated efferents.

The presence of metabolic acidosis and increased arterial alveolar oxygen tension ratio in some of our patients is consistent with the adverse consequences of brain death on pulmonary and cardiac function [24]. Novitzky et al. observed increasing anaerobic metabolism (induced by a large base deficit and low pH) in brain dead patients, leading to metabolic and hemodynamic deterioration [25]. Furthermore, it was observed that mean PaO_2 was only 209 mmHg despite measures taken during the apnea test to avoid hypoxemia. This may have been due to pulmonary problems arising secondary to intrapulmonary dysfunction, neurogenic pulmonary edema and cardiac dysfunction, all associated with head injury [26].

Prediction of the hemodynamic response is important in the evaluation of a brain dead patient, and may prevent instability. An appropriate test should minimize the incidence of hypoxemia and hypotension, which may cause irreversible cardiovascular complications or injury to transplantable organs. The mathematical equations we describe may provide a simple relationship between changes in arterial blood gases and hemodynamic variables during the apnea test. By using these equations and nomograms (Figs. 2, 4, 5) the hemodynamic changes can be anticipated, and hence cardiovascular complications or injury to transplantable organs might be avoided. Because most acutely brain injured patients are ventilated to hypocarbic alkalosis, the use of these equations becomes valuable in planning and safely executing apnea tests. However, prospective validation of the predictive power of these models is required before regular use of these nomograms. Until prospective validation is performed this model should be used as an additional piece of information for planning a safe apnea test. More importantly, this does not remove the necessity of monitoring oxygenation and hemodynamic instability constantly through the apnea test. Furthermore, if the estimated hemodynamic responses indicate a significant decrease in heart rate or blood pressure in any patient, appropriate measures should be ready, or the apnea test should be postponed.

In conclusion, the apnea test should be conducted in children as part of the clinical evaluation of brain death. On-line monitoring of oxygenation and continuous measurement of pulse and blood pressure should be performed throughout the test. When proper precautions including estimated hemodynamics are taken, the test is performed effectively and more safely.

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