Apnea testing in the diagnosis of brain death

Clinical and physiological observations

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The absence of spontaneous respiration is a crucial determinant in the diagnosis of brain death, but standardized criteria for apnea testing have not been established. Guidelines are proposed based on the results of 51 apnea tests and associated physiological measurements. In patients who fulfilled all other conventional criteria for brain death, three exhibited non-repetitive back arching and shoulder shrugging when CO₂ pressures reached 41 to 51 mm Hg during apnea testing. These respiratory-like movements were ineffective for ventilation and were not reproducible on the following day at the same or higher pCO₂. The nature of these movements, evoked potential testing, and autopsy results suggest that they were not triggered by normal medullary centers, and that these patients were, in fact, brain-dead. In four other patients with severe brain damage sparing only the medulla, normal spontaneous ventilation resumed at CO₂ pressures of 30 to 39 mm Hg (mean 34 mm Hg). High arterial oxygen tension raised this apnea point slightly, but spontaneous breathing always began at CO₂ pressures lower than 40 mm Hg. This level is therefore adequate to stimulate medullary respiration in patients with severe brain damage who are not brain-dead. In brain-dead patients, pCO₂ rises slowly during apnea (2.58 ± 0.85 mm Hg/min), in part because CO₂ production is diminished (1.8 ± 0.23 ml/min/kg). These data allow estimation of a desired length of an apnea test and standardized interpretation of results.

KEY WORDS: brain death □ apnea □ respiratory physiology □ head trauma □ medulla

Clinical Material and Methods

Fifty-one apnea tests were performed in 36 patients, aged 17 to 66 years (mean 38 years) in the neurological-neurosurgical intensive care unit. These patients fulfilled all other conventional criteria for brain death prior to apnea testing, namely, absence of all of the following: electrocerebral activity (one patient’s electroencephalogram showed severe continuous generalized slowing), pupillary light reaction, calorically induced eye movements, and response to painful stimuli. Seventeen patients had suffered head trauma, eight subarachnoid hemorrhage, seven intracerebral hemorrhage, two hypoxic encephalopathy, one tumor, and one meningitis. Core temperatures were between 36.9°C and 38.8°C. Indwelling arterial catheters were available for rapid, timed blood gas sampling.

All apnea tests were performed by the same two examiners. A stopwatch was used to time apnea and
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blood gas sampling; time intervals were accurate to within 2 seconds. An examiner placed his open hand lightly on the patient's anterior thorax to detect spontaneous respiration, and a Wright spirometer* was placed at the end of the endotracheal tube in order to measure tidal volume. The test was terminated if the examiner detected respiratory movements or if blood pressure changed more than 10%, indicating that hypoxia was occurring. At the beginning and end of each test, 3 ml of arterial blood was drawn into heparin-coated glass syringes and immediately placed on ice for blood gas determinations. Production of CO₂ was measured by collecting expired gas during mechanical ventilation in a 60-liter Douglas bag for 3 minutes and analyzing the collection on a mass spectrometer.† Three techniques were used to maintain adequate pO₂ during apnea testing: preoxygenation with 100% O₂ for 5 minutes, tracheal catheterization with 10 to 12 liters/min, or both.

Blood gas and pH determinations were performed on a Corning 165 blood gas analyzer‡ within 15 minutes of sampling and corrected for body temperature. To determine the accuracy of blood gas measurements, duplicate samples drawn less than 4 seconds apart were sent to the clinical laboratory at the end of 12 apnea tests. Interpair variability of pCO₂ measurements was between 1 and 12 mm Hg (mean ± standard deviation was 4 ± 3 mm Hg, p < 0.001 for difference between pairs) and for pH between 0.01 and 0.02 (mean variability 0.01, no difference between paired samples). These data suggest that estimates of important pCO₂ measurements should incorporate approximately 4 mm Hg in possible instrumental error.⁶

Results

Two types of respiratory movements were observed during apnea testing: abnormal respiratory-like movements that were ineffective for ventilation, and normal spontaneous respirations.

Spinal respiratory-like movements consistent with brain death were seen in three patients. These patients, who were brain dead by all other conventional criteria, made spontaneous respiratory-like movements at pCO₂ and pH values of 51 mm Hg and 7.12, 41 mm Hg and 7.14, and 41 mm Hg and 7.42, respectively. Combinations of shoulder elevation and adduction, back arching, and slight intercostal expansion were noted, but there was no clavicle elevation or abdom-

† Douglas bag manufactured by Warren E. Collins Corp., 220 Wood Road, Braintree, Massachusetts.
‡ Corning 165 blood gas analyzer manufactured by Corning Medical and Scientific, 63 North Street, Medfield, Massachusetts.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
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<tbody>
<tr>
<td>pCO₂ rise (mean ± SD)</td>
<td>2.58 ± 0.85 mm Hg/min</td>
</tr>
<tr>
<td>pH drop (mean ± SD)</td>
<td>0.02 ± 0.01/min</td>
</tr>
<tr>
<td>mean pH/pCO₂ change</td>
<td>0.006/mm Hg</td>
</tr>
<tr>
<td>CO₂ production/kg (non-lean wt)</td>
<td>1.84 ± 0.23 ml/min/kg</td>
</tr>
<tr>
<td>CO₂ production vs pCO₂ rise</td>
<td>r = 0.58</td>
</tr>
<tr>
<td>initial pH vs pCO₂ rise</td>
<td>r = -0.40</td>
</tr>
<tr>
<td>initial pH vs pH drop</td>
<td>r = 0.49</td>
</tr>
</tbody>
</table>

The laboratory data that supported the diagnosis of brain death in these three patients included: 1) median nerve somatosensory evoked potentials which showed brachial plexus potentials but absent B-waves, suggesting damage at the cervicomedullary junction in two patients; 4) auditory evoked potentials with high-amplitude click stimulation, demonstrating absent eighth nerve and subsequent responses in all three patients; 3) intracranial pressure exceeding mean arterial pressure in one patient; and 4) pathological changes typical of brain death in two autopsies performed within 48 hours.

Four patients had clinical and electrophysiological signs of hemispheric, midbrain, and pontine destruction, but resumed relatively normal breathing during apnea testing, indicating preserved medullary function. In seven apnea tests, first normal breaths occurred at CO₂ pressures of 30, 30, 33, 34, 36, 37, and 39 mm Hg, respectively (mean 34 ± 3 mm Hg). Unlike the patients described above, breathing was normal, rhythmic, and effective for ventilation. In three patients tested, arterial O₂ pressure of greater than 150 mm Hg was associated with the onset of breathing at a slightly higher pCO₂, but in no instance was the apnea point above 39 mm Hg (Fig. 1). These patients all survived for several days to 3 weeks with stable, unsupported blood pressure.

Excluding the four patients not brain-dead, only two patients failed to reach a pCO₂ of 40 mm Hg (adequate to stimulate normal respirations). Four tests were terminated because of a 10% change in pulse or blood pressure but had reached CO₂ pressures greater than 50 mm Hg.

In 44 apnea tests (Table 1), the mean increase in pCO₂ was 2.6 ± 0.9 mm Hg/min (Fig. 2), and the concomitant drop in pH was 0.02 ± 0.01/min. Mean
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**FIG. 1.** Graph showing pCO₂ at which normal breathing began with low and high oxygen tension in three patients with severe hemispheric and brain-stem damage that spared the medulla. Numbers in parentheses are pO₂ (mm Hg) at the end of each test.

**FIG. 2.** Histogram and Gaussian distribution of pCO₂ increase per minute during 44 apnea tests in 32 brain dead patients.

**FIG. 3.** Graph showing drop in pH during apnea tests in relation to pH at the start of the apnea test. Alkalosis, usually due to therapeutic hyperventilation, alters pH change/minute (and similarly pCO₂ change/minute), but the slope of the regression line is small. Dotted lines are 1 standard error from best fit regression line.

pH drop per rise in pCO₂ was 0.008/mm Hg. Initial pH affected the rate of pCO₂ rise \( r = -0.4, p < 0.01 \) and the rate of pH drop \( r = +0.5, p < 0.01 \), Fig. 3. Therefore, patients who were alkalotic at the onset of an apnea test had a more rapid rise of pCO₂ and drop in pH. The slope of the regression line and the magnitude of this effect, however, were small (Fig. 3).

Production of CO₂ in six patients was 142.0 ± 52.9 ml/min, or 1.84 ± 0.23 ml/min/kg (non-lean weight). Production of CO₂ was closely related to weight \( r = +0.9, p < 0.001 \), Fig. 4/ left), and somewhat related to pCO₂ increase/minute \( r = +0.6, p < 0.001 \). The variability in pCO₂ increase/minute among different patients was therefore only partly related to differences in CO₂ production.

**Discussion**

Small-volume, nonrepetitive, respiratory-like movements resembling posturing can occur during apnea testing for brain death. These thoracic movements have an abnormal mechanical appearance, do not effect ventilation, are unrepetitive, are not reproducible, and are associated with other data, including evoked-potential findings and autopsies consistent with brain death. These movements are probably spinal rather than medullary in origin.

For useful interpretation of apnea tests, one must identify the pCO₂ end point above which spontaneous respiration is unlikely to resume. Levels of pCO₂ adequate to stimulate respiration may vary with the particular disease or physiological state. In encephalopathic and anesthetized subjects, post-hyperventilation apnea persists until pCO₂ reaches approximately 30 mm Hg, but patients with structural brain disease may require higher levels before spontaneous respiration resumes. Our results support the notion that higher than normal pCO₂ levels are required in the severely brain-damaged patient, but the levels we indicate are considerably lower than the 50 to 60 mm Hg that others have stipulated.

One of the reasons for this disparity is that patients described in the literature who “breathed” during apnea testing for
brain death made small primitive shrugging-like movements, or the nature of their movements was not noted, either case resulting in inaccurate identification of suggested pCO₂ end points.

In patients with severe brain damage sparing only the medulla (indicated by normal respirations), breathing began at CO₂ pressures under 40 mm Hg. This level, therefore, seems conservatively adequate to stimulate medullary breathing in patients who satisfy other brain-death criteria. This "apnea point" is similar to reported pCO₂ levels at the time of the first post-hyperventilation breath in patients with less severe but bilateral nervous system damage. Incorporating a mean instrumental error in pCO₂ measurement of 4 mm Hg, we suggest that 44 mm Hg be used as the minimum desired end point for apnea testing for brain death.

In patients whose condition otherwise simulated brain death but who breathed normally, high oxygen tension raised the apnea point, but not above a pCO₂ of 40 mm Hg. Although hyperoxia makes only a small difference, it is desirable to maintain close to normal oxygen levels to insure that breathing begins at the lowest possible pCO₂. Adequate but not excessive diffusion oxygenation can be sustained for up to 10 minutes in most patients by tracheal cannulation with O₂ at 12 liters/min and is preferable, in our experience, to preoxygenation by mechanical ventilation with 100% O₂. A few patients with parenchymal lung disease who required high inspired oxygen tension would not maintain arterial pO₂ above 50 mm Hg with either method of oxygenation, and only brief apnea tests were tolerated.

Mean pCO₂ increase and CO₂ production during apnea were lower in our patients than has previously been reported in anesthetized and other patients who were not brain-dead. This may have resulted from the loss of the brain's CO₂ production and from complete muscle relaxation which also diminishes CO₂ production. Longer apnea tests will also produce lower mean pCO₂ because pCO₂ rises most rapidly during the first minute.

Examiners frequently neglect to observe patients closely enough to detect small-volume breaths. Although crude, palpation by a hand resting lightly on the thorax can be as sensitive as a flow-dependent spirometer in detecting these small movements. Care should be taken not to confuse cardiac motion, which occasionally produces a prominent impulse on the motionless chest, with small-volume respirations.

The apnea test may be performed by disconnecting the respirator at existing settings and providing diffusion oxygenation. A desired period of apnea is estimated, based on a target pCO₂ of 44 mm Hg and an expected rise of pCO₂ of approximately 2.5 mm Hg/min. After this length of time, an arterial blood gas sample is obtained, the patient is again ventilated, and if pCO₂ is above 44 mm Hg, the test may be said to be a satisfactory demonstration of apnea.

References
4. Goldie W, Chiappa KH, Young RR, et al: Brainstem auditory and short-latency somatosensory evoked re-

FIG. 4. Left: Production of CO₂ in relation to weight (non-lean). There is a close correlation. Right: Production of CO₂ in relation to rate of rise of pCO₂/minute. Dotted lines are 1 standard error from best fit regression line.

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