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The Historical Trajectory of the Apnea Test in Brain Death Determination

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In classical antiquity, absence of breathing was a less trusted sign than the absence of a heartbeat. The thinking at the time was that breathing regulated the heat of the heart. The anatomist Jacques Bénigne Winslow is credited with more serious attempts at defining death in his 1746 thesis, *Uncertainty of the Signs of Death,* but did not consider lack of respiratory movements as infallible signs. He not only irrigated the nostrils with juices of onions garlic and horse radish but also tried to stimulate tickle by the quill of a pen or a pointed pencil thrust up the nose.

It is self-evident that being unable to breathe leads to circulatory arrest. In patients with brainstem destruction, breathing often stops before the heart stops. When there is no breathing drive and no other signs of recoverable brain function are present, it is a medical scientific certainty that the patient is dead (not "with reasonable medical certainty," as the courts would like to say). So physicians need to know if the patient has a breathing drive—either spontaneous or after strong stimulation of the respiratory centers. This has become known as the "apnea test." (The test is positive when there is a negative result).

Many earlier investigators simply called apnea an absence of spontaneous breathing. Schafer et al. already noted a quite remarkable variability in their landmark paper published in 1978 "The 1968 Harvard committee recommended 3 min, a 1971 Minnesota statute, 4 min, Plum and Posner 7 to 10 min; the Conference of Royal Colleges and Faculties of the UK 10 min; and the Northwestern University criteria, 15 min" [1]. Moreover, the 1977 National Institutes of Health (NIH)–sponsored Multicenter U.S. Collaborative Study of Cerebral Death defined apnea as "no overriding of the ventilator or disconnection for 3 min" [2]. (The investigators felt it was "hazardous to an already damaged brain to undergo such tests for 3 min or more.") Also, apnea was only considered when the patient was fully supported on mechanical ventilation for at least 15 min and made no effort to override the ventilator. (Disconnection time was not stipulated.) Remarkably, after testing only three patients, Shafer and Caronna recommended an arterial pCO_2 threshold of 60 mmHg [1]. These patients started to breathe at levels varying from 45 to 56 mmHg (five trials total). This arterial pCO_2 threshold became readily accepted but was challenged by Ropper et al., who found much lower breathing thresholds in four patients; these varied from 30 to 39 mmHg (seven trials) [3]. Levels of $PaCO_2$ adequate to stimulate respiration may vary with the physiological state. In encephalopathic and anesthetized subjects, post-hyperventilation apnea persists until arterial pCO_2 reaches approximately 30 mmHg [4]. Thus, theoretically, too low an arterial pCO_2 (e.g., <30 mmHg) would mean insufficient stimulation of the impaired respiratory centers; too high an arterial pCO_2 (e.g., >100 mmHg) would depress possible brain function through CO_2 narcosis. The American Academy of Neurology guideline settled on this 60 mmHg $PaCO_2$ threshold [5].

Apnea test protocols in some parts of the world differ significantly from the US. In the UK, the patient is preoxygenated with 100% oxygen for 5 min, and a blood test confirms that arterial oxygen saturation (SAO_2) and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) correlate with peripheral capillary oxygen saturation (SPO_2) end-tidal carbon dioxide ($ETCO_2$). When an oxygen saturation of $\geq 95\%$ is reached, the respiratory rate is reduced to produce a rise in $PaCO_2$. $PaCO_2$ is

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allowed to rise above 6.5 k Pa (approximately 49 mmHg) to generate a pH < 7.4. Then, the patient is disconnected and observed for 5 min, while oxygen is insufflated at 5 L/min through an endotracheal catheter. If no spontaneous respiratory activity occurs after 5 min, the apnea test is considered positive. Elsewhere (in Japan, for example), the apnea test can only be performed after loss of seven brainstem reflexes and after isoelectric EEG.

Clearly, tweaks have been introduced in apnea testing across the globe, and not every apnea test protocol uses a $PaCO_2$ target. In the first comprehensive, world-wide evaluation of apnea testing in 2002, it appeared that 40% of protocols guidelines did not recommend using a pCO_2 target value to measure the presence of apnea, and even the pre-oxygenation with 100% oxygen, followed by a 10-min disconnection period was mentioned in less than a third of the protocols [6].

How did this test (and its "accepted" parameters) originate? Why do we most often test for apnea using an oxygen insufflation–diffusion technique? What is the historic background to the apnea test procedure, and what are the scientific underpinnings? A number of intertwining observations made this test possible. What was needed was an understanding how breathing is chemically regulated (the discovery of chemoreceptors in the medulla oblongata) and how to responsibly make chemical changes which would be recognized by the chemoreceptors (induction of hypercarbia at the bedside).

The discovery of chemoreceptors in the medulla oblongata showed us how hypercarbia stimulates these centers. Chemosensors are vital to control the alveolar ventilation necessary for blood-gas homeostasis, but they contribute relatively little to shaping the breath-by-breath pattern of respiratory movements. Mitchell first described the location of medullary CO_2 chemosensitivity at the annual American Physiologic Society meetings in 1961 and 1962, and in 1963, Mitchell and jointly published the discovery with Loeschcke [7, 8]. The central chemoreceptors occupy a position on the ventrolateral medulla of the brainstem and serve as the primary sensors for alterations in pCO_2 or H + ion concentration of the arterial blood or cerebrospinal fluid [9]. In the early 1950s, Leusen observed the effect of perfusion of the ventriculocisternal system with artificial CSF of high pCO_2 and low pH increased ventilation in anesthetized dogs. Application of “mock” CSF with a high pH, cold CSF with a normal pH, or procaine rapidly diminished ventilation [10]. A detailed examination of the ventilatory responses to these CSF perturbations led to the hypothesis that the values of pH, pCO_2, and HCO_3 content in the ECF near the ventral surface of the brainstem are important variables in determining ventilatory output.

The discovery that hypercarbia follows apneic diffusion oxygenation (ADO) was a crucial, albeit a fortuitous, finding. Comroe [11] and others in a number of unrelated (aviation research) experiments showed that insufflation of oxygen at the level of the division of the two main bronchi provides inadequate alveolar gas exchange. In apneic animals during insufflation, a wholly inadequate CO_2 elimination took place. Holmdahl also confirmed the ineffectiveness of continuous endotracheal insufflation in eliminating CO_2 during apnea (“no measurable amount of CO_2 is eliminated from the alveolar space to the external air during a one hour period of ADO”) [12]. On the other hand, the driving force of pulmonary uptake of oxygen during apnea is a partial-pressure gradient across the alveolar membrane causing diffusion of O_2 into blood. Maintenance of this gradient depends on the replacement of O_2 diffusing from the alveoli into the lungs. Holmdahl was able to perfect apneic oxygenation diffusion in number of situations such as electroconvulsive therapy, during induction of anesthesia, and with bronchoscopy [12].

Both Michaud and Pitts can be credited. Apneic-diffusion oxygenation to test apnea in brain death was first reported by Milhaud et al. in 1974 [13]. Forty patients were tested for only 15 min to limit the development of severe hypercapnia associated acidosis. As expected, marked acidosis was recognized as potentially causing cardiac arrhythmias and myocardial depression. In their study, Pitts et al. study claimed safety and relative ease of the procedure. Oxygenation could be easily maintained and $PaCO_2$ did rise predictably (Fig. 1) [14].The study established 5 min of apnea was not sufficient for an adequate $PaCO_2$ rise and 10 min

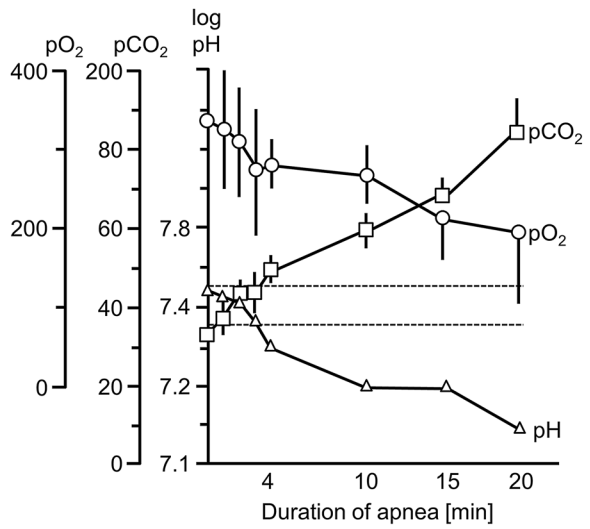

Fig. 1 Apnea test and changes in blood gas in Pitt’s study in brain death (A, B) (*Used with permission*)

was needed in most patients to reach $PaCO_2$ levels more that 60 mmHg which was again assumed a more than adequate stimulus. One patient with severe pulmonary edema underwent an apnea test, but rapid deoxygenation and cardiac arrest occurred after 5 min of apnea. Moreover, many patients had marginal blood pressures before the procedure.

Remaining Uncertainties

How death was determined in hospitals was unclear, but death determination all changed when patients with catastrophic brain injury were intubated and their breathing was fully supported by mechanical ventilators. Once no responsiveness and absent brainstem reflexes were found, breathing by the patient could only be assessed by briefly shutting-off the machine. Historically relevant, three major observations made the apnea test in brain death possible. First, oxygen administration kept the patient stable. Second, CO_2 could rise with continuous oxygenation and was not washed out. Third, the CO_2 chemoreceptors (and indirectly H + chemoreceptors) present in the medulla oblongata were established as a target. Clinical testing followed and was highly successful once procedures were in place [5].

A number of uncertainties remain, and apnea physiology studies in brain-dead patients have remained virtually nonexistent. For useful interpretation of apnea tests, one must identify the $paCO_2$ endpoint above which spontaneous respiration is unlikely to resume. Virtual all apnea tests show apnea. Breathing during the apnea test, done after all brainstem reflexes are absent, is so rare that three decades of frequent brain death determinations would yield only a handful of patients (My own 30-year experience has been with 7 patients in over several hundred apnea tests, and they all took a breath shortly after disconnection and thus with a normal $PaCO_2$). Arguably, once the patient is disconnected at a normal or elevated pCO_2 and does not breathe, he or she is unlikely to do so later. Subjecting the patient to possible hypotension, cardiac arrhythmia (from acidosis), and hypoxemia (from abnormal diffusion due to lung edema) is an unnecessary risk, albeit a small one with adequate precautionary measures. Pitts' study clearly identified circumstances that could put tested patients at risk of hypoxemia and even cardiac arrest. The study's "side effects" led to the precautionary measures used in the current AAN guideline. Although the CSF physiology in patients undergoing the apnea test remains understudied, CO_2 and acidosis stimuli to the CO_2 sensors and H + respiratory sensors in the medulla oblongata and pons make good physiologic sense. It is irrespective of what method is used to provide oxygen and its 'byproduct' carbon dioxide to the patient [15].

Conflicts of Interest

The author declares that he has no conflict of interest.

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References

1. Schafer JA, Caronna JJ. Duration of apnea needed to confirm brain death. Neurology. 1978;28(7):661–6.
2. An appraisal of the criteria of cerebral death. A summary statement. A collaborative study. JAMA. 1977;237(10):982–6.
3. Ropper AH, Kennedy SK, Russell L. Apnea testing in the diagnosis of brain death. Clinical and physiological observations. J Neurosurg. 1981;55(6):942–6.
4. Plum F, Brown HW, Snoep E. Neurologic significance of posthyperventilation apnea. JAMA. 1962;181:1050–5.
5. Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995;45(5):1012–4.
6. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology. 2002;58(1):20–5.
7. Mitchell RA, Loeschcke HH, Massion WH, Severinghaus JW. Physiologic significance of superficial medullary respiratory chemosensitivity. Physiologist. 1961;4:74.
8. Mitchell RA, Loeschcke HH, Massion WH, Severinghaus JW. Respiratory responses mediated through superficial chemosensitive areas on the medulla. J Appl Physiol (1985) 1963;18(3):523–33.
9. Severinghaus JW. Hans Loeschcke, Robert Mitchell and the medullary CO_2 chemoreceptors: a brief historical review. Respir Physiol. 1998;114(1):17–24.
10. Leusen I. Regulation of cerebrospinal fluid composition with reference to breathing. Physiol Rev. 1972;52(1):1–56.
11. Comroe JH Jr, Dripps RD. Artificial respiration. J Am Med Assoc. 1946;130:381–3.
12. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. Acta Chir Scand Suppl. 1956;212:1–128.
13. Milhaud A, Ossart M, Gayet H, Riboulot M. The oxygen disconnecting test. A test for brain death. Ann Anesthesiol Fr 1974;15 SPEC NO 3:73–9.
14. Pitts LH, Kaktis J, Caronna J, Jennett S, Hoff JT. Brain death, apneic diffusion oxygenation, and organ transplantation. J Trauma. 1978;18(3):180–3.
15. Busl KM, Lewis A, Varelas PN. Apnea testing for the determination of brain death:a systematic scoping review. Neurocrit Care 2020. Online ahead of print.