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The Respirator Brain: A Reckoning

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The term "respirator brain" is now antiquated and was a curious choice of words. It compares well with other non-descriptives such as "critical illness polyneuropathy" or "intensive care unit delirium." To gain a better understanding of why it once was commonplace, we need to appreciate the key role that artificial (mechanical) ventilation once played in the care of patients.

The Respirator

In the late 1940s, hospitals needed many mechanical ventilators to manage the epidemic of poliomyelitis in Los Angeles. This technology was possible because of the effort of consulting engineer Ray Bennett, who invented a mechanical ventilator as an alternative to the iron lung machine. But he was part of a rapidly growing technologic innovation that led to the successful application of ventilation that forced gas into the airway at above-atmospheric pressure. A large number of volume-cycled and time-cycled ventilators came on the market while investigators continued to tinker in laboratories in northern Europe, Germany, and the UK [1]. William Ritchie Russell, for example, devised the Radcliffe respiration pump in 1953 with Edgar Schuster; it could more accurately control the amount of pressure, rate, and volume and create a waveform with rapid flow rate and rise of pressure at inspiration to force air through the tracheostomy tube [2]. Many more models followed (e.g., Engstrom in Sweden and Dräger in Germany), and even today, engineers continue to develop new types of ventilators.

The Bennett ventilator had the great advantage of being easy to operate and allowing complete access to the patient for all medical and nursing purposes. However, it proved unsuitable for use in patients requiring total assisted respiration for prolonged periods. A Bird intermittent positive-pressure respirator proved more satisfactory. The addition of the negative-pressure phase was an additional reason for considering this respirator more suitable.

The widespread introduction of mechanical ventilators also created the opportunity to intubate comatose patients with major acute brain injuries in addition to patients with acute neuromuscular disease. Once the device became available, its use exploded, not only to protect airway and provide adequate ventilation but also to manipulate acid–base balance. There was sufficient knowledge on the cerebral physiology changes with hypocarbia. But results outside traumatic brain injury were disappointing. Hypocapnia, induced and sustained by artificial hyperventilation, has no indication as a treatment in severe cases of stroke. The primary or focal lesions are irreversible, with no impact on the fatal outcome when secondary edema occurs. Another review in comatose patients was unable to separate "the effect of respirator treatment per se and of hyperventilation" in determining effect on outcome [3, 4]. Similarly, later studies in traumatic head injury were inconclusive, with ongoing concerns of harm [5]. So, inducing hyperventilation with the use of the mechanical ventilator could not be seen as a potential benefit. The mechanical ventilator became a commonly implemented intervention in the ICU and not only for patients with acute lung injury. Soon it became obvious that, once on the machine, extubation was problematic in neurologic patients.

The Respirator Brain

Mechanically ventilating patients resulted in a new state observed by neurologists and neurosurgeons; over time, brainstem reflexes deteriorated in a rostrocaudal pattern. When it reached the medulla oblongata, a sudden decline in blood pressure and loss of triggering of the ventilator signaled an absent respiratory drive. This condition became known as "respirator brain" because

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only mechanically ventilated patients presented with it. Initial case series described patients on respirators for prolonged periods, and the neuropathological effects seemed to be linked somehow to the respirator.

Many early descriptions of respirator brain did not include a detailed neurologic assessment, although the absence of movement, reflexes, cough, and breathing betrayed its extreme seriousness. Furthermore, patients with retained brainstem reflexes, such as in severe anoxic-ischemic injury, also demonstrated respirator brain. The pathophysiology is an intensive destructive process in which hydrolytic enzymes resulting in cavitation filled with liquid and caused ischemia [6]. Cystification of the brain due to liquefactive necrosis and mineralization is now rarely observed because of reduced autopsies and (appropriate) discontinuation of life support in a hopelessly injured patient or a patient diagnosed as having brain death.

Jun Kimura, one of the fathers of neuroelectrophysiology, may have introduced the term respirator brain. "So characteristic was this spectrum of changes that we have used the term 'respirator brain' for the specimens which demonstrated these findings." In his article on flat electroencephalograms, he noted that "during a 36-month period… 25 patients with clinical evidence of severe brain damage were treated with a mechanical respirator for six or more hours and eventually came to postmortem examination." Kimura et al. [7] presciently concluded, "We believe that it is useless and inhumane to maintain the patient on a mechanical respirator after this has been established."

He recognized all too well that the changes in the respirator brain were autolytic phenomena and that there was no vital reaction on the part of the tissues. Neurons and parenchyma show cytolysis and autolysis rather than ischemic change and necrosis. We now know that medulla oblongata can be perfused in some cases in respirator brain, and these patients need not be on a respirator to develop the classical neuropathological changes. Therefore, pathologists would prefer the term "nonperfused brain," which is more descriptive and pathophysiologically accurate. Mollaret noted that the microscopic neuropathologic abnormalities were "*un caractère de gravité extrême*" [8]. Nonperfused brain leads to irreversible global ischemia in which blood flow to the intracranial contents never returns. Brain circulation (except for extracerebral flow) and function can never be restored [9–11].

Computed tomography scans of the brain may already show diffuse hypodensities with loss of known structures (Fig. 1). Grossly, when lifted from the skull at autopsy, the nonperfused brain shows a dusky brown discoloration of the cerebral cortex, blurring of the junction of the cortex

Fig. 1 Computed tomography scan showing massive hypodensities as a result of a nonperfused brain

Fig. 2 Autolytic liquefaction

and the white matter, and general friability of the brain (Fig. 2). There is increasingly brown discoloration of the entire brain. Cerebral tissue is difficult to fix in formalin due to protein alterations, resulting in symmetrical patches of pink, unfixed white matter in the regions of the centrum semiovale most distal from the ventricles. The pathological changes of a nonperfused brain develop within 12 h, although they become more obvious in 24 h, a crucial point for the neuropathologist called to confirm brain death. Microscopically, the histology is far better preserved than expected from the gross appearance. Although acidophilic neurons may be seen, this is not the rule, and neuronal cell membranes are preserved. There is a general pallor of the tissue, which stains poorly. Stagnant red-blood corpuscles are seen microscopically in the circulation, appearing pale due to lysis of hemoglobin. Because of the lack of perfusion,

Table 1 Neuropathology in coma and brain death (adapted from Walker [13])

Parameter	Grade 1 (slight)	Grade 2 (moderate)	Grade 3 (severe)
Macroscopic consistency, localization, color	Soft, circumscribed, yellow	Soft, extensive, yellow–brown	Semiliquid brain, yellow-green
Microscopic			
Staining quality	Poor	Very poor	Minimal
Ground substance	Darkly stained	Darkly stained	Pale
Edema	Perivascular	Generalized	Intracellular
Vessels	Engorged	Lysed red-blood cells	Necrotic and loss of structures
Neurons			
Cytoplasm	Meta- and hyperchromatic loss of Nissl bodies	Metachromatic homogeneous, pale or darkly stained, vacuolated and granular	
Nucleus	Eccentric	Pyknotic or pale and vacuolated	Pyknotic and fragmented
Glia	Swollen	Swollen, vacuolated with pyknotic nucleus	Liquefied and foamy
White matter	Myelin preserved	Swollen, fragmented	Edematous, swollen myelin, irregular axons

there is no tissue reaction except possibly at the border of perfused and nonperfused tissue, usually at the level of the high cervical spinal cord or medulla oblongata. Cases of long-term survival after nonperfused brain show a leukocytic tissue reaction superficially, with white blood cells infiltrating the brain parenchyma from the perfused skull and meninges. Kramer even categorized degrees of involvement (Table 1) and introduced another term: "state of deanimation" [12, 13]. In his case description, he noted "an extensive neuronal devastation and a marked gliosis of the whole brain were found. There was an enormous destruction of the cerebral cortex, the white matter, the basal ganglia, thalamus, tegmentum of the brainstem, brachia conjunctiva, brachia pontis, corpora restiformia, and the cerebellum" [12]. He also noted that the enormous development of the brain lesions was possible during 5 months of artificial survival of the patient. It remains unclear whether the patient fulfills contemporary criteria for brain death.

Conclusions

Brain perfusion depends on the mean arterial blood pressure exceeding the intracranial pressure (ICP) to drive the blood through the resistance of the cerebral vasculature. The cerebral perfusion pressure equals the mean arterial blood pressure minus the ICP. When the cerebral perfusion pressure drops below a critical value (around 45 mm Hg), nonperfused brain can occur if flow is not restored immediately. Whatever the cause of the increased ICP, perfusion stops, and blood stagnates in the microcirculation throughout the brain. The massive loss of neuronal tissue follows. Early neuropathologists always considered artifactual findings, which may be related to time to fixation (*Plongé dans du formol*) [9], but the consistent finding convinced them of its authenticity.

We occasionally find cases with prolonged support and then find mumification of the brain or a brain in a viscous liquid state [14, 15]. Neuropathologic studies of individuals on life support for any length of time after clinical declaration of brain death are few, especially from the modern era, and generally comprise case reports or historic series of respirator brain descriptions with postdeclaration intervals between 2 and 21 days [16].

Respirator brain remains a curio from the past. We only encounter this oddity when families deny the catastrophic irreversible nature of brain injury and physicians are reluctantly forced to continue care under the most trying and dire systemic circumstances. Respirator brain is not synonymous with brain death; it is synonymous with a nonperfused brain resulting in overwhelming loss of vital neurons. Currently, once a neuropathologist encounters such a brain with brain cutting, there is a larger story to tell—a story of denial.

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