Introduction

Even more now than in the recent past, neurointensivists are asked to evaluate the effects of hypoxemia on the brain. The SARS-CoV-2 pandemic, characterized by widespread transmission and admitting patients by the thousands, requires aggressive management of profound hypoxemia. Many patients are initially in what has been called “silent hypoxemia.” A thoughtful explanation of why ‘silence’ is expected rather than unusual has been provided by Tobin et al., who emphasizes to recognize well-established physiology principles [1]. Hypoxia increases depth and rate of breathing but the carotid artery baroreceptors are set at quite low levels. Patients seldom experience dyspnea with moderate hypoxemia. This is further illustrated by the experience of climbers, in whom oxygen saturations of < 65% for prolonged periods may “dull the mind” but do not always increase the sensation of dyspnea [2]. Clinically, only a severely hypoxemic (<50%) patient is tachypneic (assuming no further blunting effect from hypercarbia or enhancing effect from fever) and restless. The gradual hypotension and rising PaCO2 are eventually more crucial factors in declining consciousness than hypoxemia alone.

Neurologists will have to anticipate an increasing number of intensive care consults during and even long after the SARS-CoV-2 pandemic is over. Specifically there will be questions about whether the brain can tolerate prolonged hypoxemia. Early neuropathology studies in SARS-CoV-2 have not found major brain damage due to hypoxemia. In a recent autopsy study of 43 patients between ages 51 and 94 years, 6 (14%) patients had new ischemic infarctions most likely due to thromboembolic events but no evidence of anoxic-ischemic injury in the examined frontal cortices [3].

Hypoxemia was already sub-classified in the 1920s [4], and it is important to distinguish between anoxic anoxia (reduced hemoglobin saturation due to pulmonary disease), anemic anoxia (reduced hemoglobin, but normal saturation in carbon monoxide poisoning), stagnant anoxia (normal hemoglobin saturation but reduced cerebral blood flow due to shock), and other less common forms. There is no question that profound hypoxemia may damage the brain, but when it does, there is often associated severe hypotension from vasodilatation (or briefly no pulse); hence, the commonly used moniker hypoxic-ischemic brain injury.

Already in the 1940’s alterations in cerebral metabolism after hypoxemia have been studied by Gurdjian et al. [5]. Cerebral lactic acid rose when the oxygen content of the inspired air fell to a critical level of 11 to 13 percent. As the oxygen percentage further decreased to a critical level of 7 percent, they noted phosphocreatine breakdown. A return to room air was followed by an extremely rapid re-synthesis of phosphocreatine, but lactic acid levels fell much more slowly.

Historically, from where did the data originate connecting hypoxemia with brain damage? What are the lessons for today?

Hypoxemia and the Brain

In the 1940s and 1950s, physiological experiments did demonstrate that unconsciousness is bound to rapidly occur when the arterial oxygen tension (PO2) is lowered to 25 to 35 mm Hg [6, 7] but also when carbon dioxide tension (PCO2) is increased to 70–110 mm Hg [8]. These and other observations resulted in the assumption that permanent brain damage occurs when the PaO2 falls to 30 mm Hg [9] and even lethal brain damage at a venous-capillary level of 12 mm Hg, although some marginal
cerebral mitochondrial function is still possible at a PO2 below 1 mm Hg [10].

Morrison’s dog and monkey study (Fig. 1) just after the Second World War [11] provided a good insight into how pure hypoxemia could harm the brain. This study with a very specific set-up—arguably to say the least—rationalized the sacrifice of a large group of animals in order to answer questions about hypoxemia: “The extensive use of the high flying airplane in war, with its accompanying hazards of failure of oxygen supply, jumps from high altitudes and the possible cumulative effect of the chronic day by day exposure to fatigue and anoxia, makes the need for such an investigation imperative”.

Morrison exposed 25 dogs in air tight chambers to episodes of atmospheres deficient in oxygen, which lasted 3 to 4 h and on average varied in number from 1 to 40. The oxygen content of the atmosphere ranged from 13% to about 4.5% using a normal inspired pressure. In addition to the dogs, the brains and spinal cords of 10 monkeys were studied. These monkeys were even longer subjected to daily anoxia in a decompression chamber. With the Nissl stain, neuropathology showed that the ganglion cells of the outer cortical layers were pale, chromatolytic, swollen, and vacuolated. Some demonstrated liquefactive necrosis. These phenomena varied from one animal to another and from location to location in the brain (Fig. 2) and involved cells of the supragranular layers in various parts of the cortex with extensive laminar necrosis, showing loss of fan fibers in the cortex (Fig. 3). The purkinje cells exhibited swelling and vacuolation but also the basal ganglia and thalami. The white matter lesions were in the subcortical areas and predominantly in the centrum semiovale. The degree and duration of anoxia were crucially important. A single, sudden exposure to a simulated altitude of 32,000 feet (10,000 m) for 25 min could produce extensive laminar necrosis in the cortex of the monkey. With repeated exposures to mild hypoxia, the first histologic changes occurred in the cell bodies of the cortical gray matter. This was seen at a level of about 12 or 13 volumes percent of oxygen in the blood.

When the percentage of oxygen was further reduced, to about 10 volumes percent, the number of exposures increased and white matter damage became more obvious: “a pattern of demyelination in the corpus callosum, the centrum semiovale and the adjacent fingers of subcortical white matter. The frontal lobe was most often involved and the temporal lobe least often. The cerebellum was more frequently affected than the basal ganglia, and the spinal cord and medulla oblongata were unaffected by any degree of anoxia compatible with life. An oxygen level of 4 or 4.5 volumes percent was about as low as a dog could tolerate”. Morrison stated that “in general, it may be said that it takes a fairly long series of exposures to a degree of anoxia which in a single exposure would be incapable of these lesions of the white matter”.

These observations were challenged 50 years ago by Gray and Horner, who published one of the first large clinical studies on in hospital survival in Yale-New Haven Hospital during 1966 and 1967 [12]. The age range of the 22 patients was 8 to 92 years. The 22 patients under study constituted 0.45% of all patients studied. The lowest PaO2 observed was 7.5 mm Hg with a simultaneous venous PO2 of 2.0 mm Hg; the patient’s course is shown in Fig. 4. The relationship between arterial PO2 and PCO2 in their study is shown in Fig. 5. Three patients with highest arterial PCO2 levels died; three with the lowest levels survived. There was no correlation between PCO2 and survival or level of alertness in the remaining patients. Nine of the 22 patients died 35 min to 2 months after the study without having been discharged to their homes “Thirteen patients were discharged in improved conditions. Of these patients, ten were fully ambulant and capable of self-care, and three had limited ambulation. Twelve of the 13 patients were still alive 5 to 20 months after the initial study; one patient had died 2½ months after discharge from the hospital”.

However, coma with decerebrate motor responses, expectedly, correlated with severe, irreversible brain damage. The neurological symptoms were attributed to hypoxemia because there was a poor correlation with hypercapnia. But two patients with decerebrate motor responses survived with no gross neurological or personality defects. Therefore, the study showed that the prognosis can be good when hypoxemia alone is the attributed cause.

Refsum concluded that a closer relationship exists between state of consciousness and arterial carbon dioxide tension, than between state of consciousness and oxygen tension or content. The highest arterial PCO2 associated with consciousness was 89 mm Hg; the lowest, arterial PO2 20 mm. Hg. According to Refsum’s observations, the oxygen and carbon dioxide abnormalities appear to be additive in their life-threatening potential [13].
HISTOPATHOLOGIC EFFECT OF ANOXIA ON THE CENTRAL NERVOUS SYSTEM

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Damage to the nervous system as a consequence of anoxia has been produced in many ways, but most of the investigations dealing with this subject have borne but slight relation to the problem of aviation. Illuminating and important as many of these previous clinical and experimental studies have been, they have not, with few exceptions, been concerned with precisely the conditions met with in aviation. The purpose of the present investigation was to determine whether histologic alterations were produced in the central nervous system after repeated, sublethal exposures to an atmosphere deficient in oxygen; to measure the amount of oxygen to which the nervous system was exposed, and to correlate that amount, if possible, with the nature of the histologic process. The extensive use of the high flying airplane in war, with its accompanying hazards of failure of oxygen supply, jumps from high altitudes and the possible cumulative effect of the chronic day by day exposure to fatigue and anoxia, makes the need for such an investigation imperative. It is well known that acute and chronic altitude sickness was a major problem in the first world war and in commercial aviation after the war; and while greatly improved precautionary measures are in use at the present time, the possibility of neurogenic deterioration among pilots and other fliers has in no sense been eliminated. An attempt has been made, therefore, to investigate the effect on the brain of repeated exposures to degrees of anoxia which in a single exposure would have but transient effect.

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1. Armstrong, H. G.: Anoxia in Aviation, J. Aviation Med. 8:84, 1938.
2. Jold, E.: Medical Problems of Aviation, J. Roy. Army M. Corps 78:1289, 1939.

The different conditions under which anoxia of the nervous system has been produced may be grouped under the classification of anoxias as suggested by Barcroft, or by Peters and Van Slyke. 1. Anoxic anoxia is characterized by low oxygen tension of the arterial blood, so that the hemoglobin does not have its normal degree of oxygen saturation. 2. Anemic anoxia is a condition in which insufficient amounts of hemoglobin are available for oxygen transport even though the oxygen tension is normal. 3. Stagnant anoxia is the result of defective circulation of blood during which the tissues fail to receive an adequate supply of oxygen even though the arterial blood contains sufficient oxygen in the proper degree of saturation. 4. Histotoxic anoxia occurs when the tissue cells themselves are unable to utilize oxygen even though it is available in the arterial blood.

As a frame of reference this classification has a good deal of practical value. Since the methods of producing the various kinds of anoxia differ from one another, the local physiologic effects on the brain are not exactly the same, and, consequently, the resulting pathologic lesions show certain variations with the different types of anoxia. While it is not always possible to identify the type of anoxia from the nature of the neuropathologic lesion, there are certain characteristic features that are of value. Without anticipating the results of this experiment, it may be pointed out, for example, that zones of laminar cortical necrosis were found in a monkey that had been subjected to anoxic anoxia in a decompression chamber and these lesions were apparently identical with those reported by Courville in cases of anoxic anoxia incident to nitrous oxide anesthesia. On the other hand,

3. Barcroft, J.: Anoxemia, Lancet 2:485, 1920.
4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 1264.
5. Courville, C. B.: Asphyxia Following Nitrous Oxide Anesthesia, Medicine 15:129, 1936.
Table 1

| Dog      | Number of Experiments | Number of Days | Oxygen in Blood, % | Lesion |
|----------|-----------------------|----------------|--------------------|--------|
| Judith   | 25                    | 33             | 13                 | +      |
| Duncan   | 23                    | 44             | 12                 | +      |
| Panzy    | 19                    | 11             | 11                 | +      |
| Lillian  | 26                    | 38             | 10                 | +      |
| White Devil | 28              | 00             | 70                 | +      |
| Snowball | 3                     | 8              | 9                  | +      |
| Casper   | 12                    | 16             | 9                  | +      |
| Allegra  | 4                     | 62             | 8                  | +      |
| Oscar    | 4                     | 6              | 8                  | +      |
| Horace   | 29                    | 29             | 8                  | +      |
| Sade     | 19                    | 33             | 7                  | +      |
| Timothy  | 16                    | 20             | 6                  | +      |
| Edwin    | 13                    | 15             | 5.5                | +      |
| Patricia | 36                    | 73             | 5                  | +      |
| Harry    | 21                    | 20             | 5                  | +      |
| Hector   | 12                    | 22             | 5                  | +      |
| Souley   | 12                    | 18             | 5                  | +      |
| Wiener   | 7                     | 11             | 5                  | +      |
| Tuck     | 29                    | 32             | 4.8                | +      |
| Terry    | 35                    | 43             | 4.3                | +      |
| Flora    | 35                    | 42             | 4.5                | +      |
| Geneville| 31                    | 41             | 4.0                | +      |
| Peter    | 12                    | 43             | 4.8                | +      |
| Victor   | 11                    | 22             | 4.5                | +      |
| Susy     | 1                     | 2.4            |                    | +      |

Fig. 2 Dog neuropathology (from Morrison used with permission)

Fig. 3 Laminar necrosis (from Morrison used with permission)

Fig. 4 Extreme hypoxemia in heroin addict (from Gray and Homer used with permission)
Conclusions

Much work has been done on the relation between hypoxemia and the vulnerability of the brain. When assessing acute brain injuries, we clearly need to distinguish purely hypoxic events from combined hypoxic and ischemic events—these very different stressors produce dramatically different pathogenesis and effects on brain. Without a doubt, even in otherwise healthy individuals, when hypoxia becomes anoxia (i.e., near anoxia) and is prolonged for an hour, circulation will fail, and ischemia will become a component of the subsequent pathology. Hypotension alters consciousness, and the mean arterial pressure when we start becoming drowsy is somewhere at a mean arterial pressure (MAP) of 50 mmHg and will cause ischemic zones in watershed areas, and the impaired consciousness may become persistent for days and weeks. (Compare these MAP thresholds with other organ systems—cardiac (coronary) MAP for adequate coronary perfusion pressure of 65 mmHg and MAP of 70 to 75 mmHg for adequate perfusion of the kidney).

Brief and profound hypoxia (Sao2 50–70% for 10 to 30 min) in healthy humans is well tolerated and not accompanied by systemic acidosis or circulatory impairment. Isolated hypoxic brain injury may involve damage to deep gray matter such as the caudate, putamen, and thalamic regions, but the recovery is more complete than the recovery following shock and hypoxemia. We can tentatively conclude from this historical review that the unearthed studies of clinical pure hypoxemia result in mostly good recoveries—there is encouraging resilience in brain structures from low oxygen vis-à-vis hypotension.

Conflicts of Interest

The author declares that he has no conflict of interest.

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