Experimental Effects of Acutely Increased Intracranial Pressure on Respiration and Blood Gases*

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ver the last 10 years there has been a growing number of clinical observations concerning the alteration of respiratory function with disease of the central nervous system.14,28,34-37,55 Within the specific field of head injury and increased intracranial pressure, improved monitoring techniques have called attention to the relationship of intracranial pressure waves and respiratory patterns.28 Equally important, and intimately related, have been the observations concerning blood gas and acid-base alterations in head injury, and their prognostic significance.5,15,53,56,55 These changes in the blood gases and acid-base balance alter the caliber of the cerebral vessels and the rate of cerebral blood flow. These in turn further increase the intracranial pressure.

Clinical observations of our own have led us to believe that alterations in respiratory pattern may well be one of the earliest signs of increased intracranial pressure, far preceding the classical symptoms of clinically observed changes in pulse and blood pressure. This paper reports an investigation of the interrelationship of intracranial pressure, respiration, and blood gases under a controlled situation, using an extradural balloon to simulate compression of an epidural hematoma.19,20 Such a model, while subject to the criticism that relatively slow compression by a balloon simulates only one form of acute injury, is nevertheless controllable and repeatable. The absence of other factors in acute injury, such as acceleration, deceleration, contusion, hemorrhage, and laceration, limits the injurious effects studied primarily to those caused by compression and its resultant distortion; the method also provides means for careful monitoring of these effects.

Materials and Methods

Thirty-three adult mongrel dogs were used, varying from 20 to 40 lbs. An extradural hematoma was simulated by a rubber balloon, placed in the epidural space through a trephine hole in the fronto-central region over the convexity, and connected to a syringe by a small polyethylene tube. The intracranial pressure was monitored by a similar but smaller balloon placed in the opposite epidural space, and connected by polyethylene catheter to a Statham strain gauge. The systems were filled with saline. Arterial blood pressure was monitored by a femoral artery catheter attached to a Statham strain gauge. Respirations were monitored by a Harvard pneumograph connected to a Statham gauge. The latter system was air-filled. Two silver wires were used to monitor a biparietal electroencephalograph (EEG). These were placed through small bony openings and rested on the dura. All skull defects were closed and the various devices fixed by applying acrylic dental cement. Recordings were made on the Beckman Dynograph.

All animals were anesthetized intravenously with Diabutal and maintained throughout the procedure on small amounts of the intravenous fluid. No additional anesthesia was needed or given during the course of compression. All animals were breathing spontaneously, but had endotracheal tubes in place. Secretions were cleared by suction periodically as needed.

Increments of fluid were added to the compressing balloon in amounts starting at 0.4 to 0.5 cc, and toward the end of compression tapering to 0.1 cc. The compression was carried out over a 2-hour period, until the animals showed evidence of cerebral vasoparesis, defined as "that state in which there is apparent loss of vasmotor tone of the cerebral vessels, as evidenced by the spontaneous rise of intracranial pressure in direct relation to, and paralleling, the sys-
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Enteric blood pressure." This state was almost always accompanied by a flat EEG and fixed, dilated pupils.

Blood samples were taken and analyzed for PaCO\(_2\), PaO\(_2\) and pH at baseline, at the clear onset of slowing and deepening of the respiratory patterns, and at vasoparesis. In addition, in 14 animals, 100% O\(_2\) was administered for periods of 3 minutes at the same stages of compression; blood gas samples were obtained before and during the administration of the O\(_2\), which was always spontaneously inspired. Thus, each of these 14 animals served as his own control for blood gases.

**Results**

The initial alteration noted after compression was begun was a slowing and deepening in respiration, which would persist even with compensation of intracranial pressure to nearly baseline levels. If the animal was under relatively light anesthesia, a brief period of hyperventilation sometimes preceded this change (Figs. 1 and 2).

As compression continued, the respirations became deeper and less frequent (Fig. 3). By the time vasoparesis was clearly evident, they were occurring at intervals of 1 minute, either as single great gasps or bursts of two or three respirations in "decrescendo" order (Fig. 4). The intracranial pressure and blood pressure at this stage clearly showed waves correlated with the respirations. At the same time, the EEG would become flat bilaterally, and both pupils fixed and dilated. If at this point the pressure was not promptly relieved, the respirations would cease quite abruptly; the blood pressure and intracranial pressure would then fall and the animal would die.

The PaO\(_2\), PaCO\(_2\), and pH samples obtained from the femoral artery during compression are shown in Table 1. Since each dog serves as his own control, the variation in baseline values from dog to dog can be disregarded. In 76% of the animals there was a drop in PaO\(_2\), and in 78% a rise in PaCO\(_2\), by the time the respirations were clearly slower and deeper. The pH at this

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**Fig. 1.** Baseline and initial compression. Top line indicates minutes at slow speed (25 mm/min) and seconds at fast speed (25 mm/sec). Pressure calibrations are in mm Hg. Arrows above ICP line indicate increments of 0.2 cc fluid in compressing balloon. Arrows above respiration line indicate start and stop of administration of 100% O\(_2\). No change is seen in respiration. Note speeding of respirations with compression.
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Fig. 2. Initial compression; data as in Fig. 1. Note slowing and deepening of respirations with increasing compression.

time either remained the same or showed a slight tendency to fall.

In the clearly vasoparetic stage, the PaO₂ had fallen markedly, being below 60 mm Hg in 91% of the dogs. The PaCO₂ had risen in all cases, but not so dramatically, being over 40 mm Hg in only 50% of the animals, and over 45 mm Hg in only 36%. The pH fell slightly in all but one case. Table 2 shows the effects of allowing the animal to breathe 100% O₂ spontaneously. In all but two animals the PaO₂ rose. At baseline, the rise in PaO₂ was paralleled by a rise in the PaCO₂, but after the onset of respiratory slowing and at vasoparesis, the PaCO₂ rose in only 50% of the animals. The pH changes during the period of added O₂ were small and inconsistent.

The changes in respiratory patterns while the animal was breathing 100% O₂ are shown in Figs. 1, 4, and 5. The increasing tendency of the added O₂ to cause apnea as compression increased and respirations slowed was dramatic, and entirely consistent in all the animals.

Central Mechanisms for Respiratory Control

The central control of respiration is exceedingly complex, and we have made an attempt in Fig. 6 to summarize some major features of its organization. For convenience these may be divided into neural and chemical mechanisms.

Neural Mechanisms. The basic neural mechanisms consist of an inherently rhythmic medullary center, which is modified or overridden by a rostrally placed apneustic center. The latter, in turn, is modulated by impulses from the still more rostral pneumotaxic center, or from vagal afferents of pulmonary stretch receptors and other peripheral reflexes.⁷,¹²
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Other centers, yet more rostral, may influence these basic centers. These include areas of central gray in the midbrain, which affect respiratory frequency and depth apparently via a facilitatory-inhibitory action on the reticular activating system.\textsuperscript{12,13}

The hypothalamus, especially the lateral portion, also has an important influence on respiration. Stimulation results in increased frequency, and often depth, while lesions result in the reverse. The more lateral lesions may result in reduced frequency and increased depth on occasion.\textsuperscript{12,38,39}

Finally, stimulation of the ventral frontal lobe, insula, lateral temporal pole, and the most anterior portion of the cingulate gyrus have been observed to inhibit respiration. Respiratory facilitation occurs with stimulation of the motor cortex, Sylvian gyrus, and middle cingulate gyrus.\textsuperscript{12}

Chemical Mechanisms. The chemical sites of action are divided into the central and peripheral chemoreceptors. The peripheral chemoreceptors are sensitive to changes in the PaO\textsubscript{2}, and are located at the carotid bifurcation and aortic arch, and possibly along other blood vessels. Afferents of the carotid receptors pass along the glossopharyngeal nerve, and those of the aortic arch via the vagus. A drop in the PaO\textsubscript{2} results in increased respiratory drive while a marked increase will reduce it.\textsuperscript{2,8-10,35,66} The degree of response is dependent on a number of variables, however, such as pre-existing levels of PaO\textsubscript{2}, PaCO\textsubscript{2}, and pH at the time of any change, and there appears to be a mechanism of interaction between the PaO\textsubscript{2} and PaCO\textsubscript{2} levels.\textsuperscript{1,2,6,49,58}

Central chemoreception is primarily via PaCO\textsubscript{2} or brain interstitial pH as influenced by the PaCO\textsubscript{2}, in chemoreceptors probably lying in the floor of the lateral portion of the fourth ventricle. A rise in PaCO\textsubscript{2} is followed by increased respiratory drive, while a fall is accompanied by reduced ventilation. Again, the interrelation of the PaCO\textsubscript{2} and PaO\textsubscript{2}, or state of the central nervous system, such as sleep, may all influence the degree of response.\textsuperscript{12,40}

Lesions of the Respiratory Mechanisms

Lesions of Neural Mechanisms. Plum, in a series of papers,\textsuperscript{3,35-37} has attempted to correlate alterations in respirations observed
in a variety of clinical situations with anatomical lesions. In the case of compression he has described a spectrum of respiratory changes beginning with sighs and yawns, progressing to a Cheyne-Stokes pattern, possibly followed by a period of hyperventilation. Next, there develop pauses and, finally, deep sighs and gasps. He associates these changes with progressive functional destruction of respiratory control in a rostral to caudal direction. The final stages of deep gasps and sighs, disorderly clusters of breaths, or, finally, slow gasping, all-or-none respirations represent for him medullary compression. He finds that the respiratory center at this stage is hyposensitive to chemical drive. He states that it is typical of medullary compression that respiration fails before circulation and that such changes are more often due to trauma, or rapidly expanding hemorrhage, than to ischemia or degeneration. Cook, et al., have drawn attention to similar respiratory changes in head injury patients.

Lesions of Chemical Mechanisms. Under normal circumstances, the primary chemical control of respirations is to be found in the central, or PaCO₂-pH, receptors. The peripheral or PaO₂ sensitive receptors are clearly active only when the PaO₂ has fallen to levels of 60 mm Hg, with accentuation of their effect if the PaCO₂ is simultaneously elevated. Lesions of the central chemoreceptors may take two broad forms. The first, a lessening of their sensitivity of relatively slight degree, results in slight rises of the PaCO₂ and slight falls in the PaO₂. Such decreased sensitivity is thought to be secondary to depression of the reticular activating system, and has been observed in sleep and anesthesia, or following direct lesions of the midbrain reticular activating system. The response, although depressed in these circumstances, is not lost.

The second form of alteration in central chemoreception appears to be the result of direct damage to chemoreceptor centers in the region of the fourth ventricle. A syndrome of hypoventilation secondary to brain stem dysfunction has been described by sev-
eral writers$^{31,37,41-43}$ and is characterized by hypercapnia, hypoxemia, somnolence, and a lack of normal respiratory response to increased arterial CO$_2$. The peripheral PO$_2$ receptors then become of prime importance. Adding oxygen in this, and related states of central depression such as emphysema, barbiturate excess, or narcotic excess, then results in reduction of respiration by removing the hypoxic drive, while the PaCO$_2$ rises. Only in rare circumstances have such changes in response been noted in the absence of disease.$^4$

Our own results tended to show a rostral to caudal failure of respiratory controls similar to that described by Plum and Posner.$^{36}$ We observed early a steadily progressive downward course of increasing depth and slower rate with intermittent deep sighs, occasionally preceded briefly by hyperventilation. These changes in respiratory rate were correlated with slight falling of the PaO$_2$ and raising of the PaCO$_2$ Evidence that these changes accompany decreased central CO$_2$ sensitivity of chemoreceptors was found in the increased apneic response to O$_2$ (Figs. 1 and 5). Furthermore, these changes preceded obvious changes in blood pressure or pulse (Figs. 1–3).

It seems reasonable to us that the common mechanism in these changes is a depression of the reticular activating system, since lesions of this system have been shown to effect similar changes in both respiratory pattern and chemoreceptor sensitivity.$^{12,13,21,40}$ Schneidoff et al.$^{45}$ have shown similar drops in O$_2$
TABLE 2

Effect of added 100% O₂ on PaO₂, PaCO₂, and pH at varying stages of compression

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Baseline</th>
<th>Spontaneous Resp. for 2 Min. of 100% Oxygen</th>
<th>Clear Slowing and Deepening of Respiration</th>
<th>Spontaneous Resp. for 2 Min. of 100% Oxygen</th>
<th>Onset of Marked Vasoparesis</th>
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<tr>
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<td>Spontaneous Respiration Room Air</td>
<td>Spontaneous Resp. for 2 Min. of 100% Oxygen</td>
<td>Spontaneous Respiration Room Air</td>
<td>Spontaneous Resp. for 2 Min. of 100% Oxygen</td>
<td>Spontaneous Respiration Room Air</td>
</tr>
<tr>
<td></td>
<td>PaO₂</td>
<td>PaCO₂</td>
<td>pH</td>
<td>PaO₂</td>
<td>PaCO₂</td>
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<td>36.5*</td>
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<td>37.0</td>
<td>7.38</td>
<td>75.0*</td>
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</table>

* Dubious values.
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FIG. 5. Demonstration of slowing and deepening of respiration with added O₂. Compare with Fig. 1.

saturation following concussion in dogs. They and others 18,31,33,50,53 have confirmed the occurrence of similar arterial O₂ drops in the human after head injury.

In the later stages of compression we noted deep irregular gasps with long apneic pauses. This pattern was associated with the onset of vasoparesis, or self-sustained rise in intracranial pressure, and extremely low PaO₂ values. At the same time there was markedly increased sensitivity to inhaled O₂ as noted by an increased apneic response (Fig. 4).

We attribute these changes in respiratory drive to direct medullary compression, resembling, as they do, the findings noted in various forms of lower brain stem dysfunction. 3,12,34-37,41,43 The very low PaO₂ levels in the face of high normal PaCO₂ levels and the marked apnea after O₂ administration give evidence that the respiratory drive is primarily from hypoxia via peripheral chemoreceptors. How complete the switch to a peripheral hypoxic drive is, no doubt varies from animal to animal, but it may be that the onset of gasping respirations signals this shift in drive.

Thus, a cycle can be pieced together. We conclude that, under the conditions of our experiment, respiratory changes precede significant changes in the vascular bed, occurring before a very marked change in intracranial pressure. This alteration is accompanied by progressive reduction of chemoreceptor sensitivity and concomitant changes in blood gases. The resultant hypoxia and ischemia, though mild, may contribute to loss of vascular tone and consequent further increases in intracranial pressure. At a late stage marked decrease in central chemoreception, resulting in a hypoxic drive, undoubtedly causes further deterioration in respiration and blood gases.
Others have shown that such alterations in respiratory pattern lead to increased intracranial pressure\textsuperscript{25,26,30} while control of respirations may reverse such increases.\textsuperscript{25,27,29} Further, the chemical effects of altered respiratory function have been shown to alter the size of cerebral vessels and the cerebral flow, with hypoxia, hypercarbia, and increased acidity leading to dilatation of the vessels with increase in flow, while hyperoxia, hypocarbia, and alkalinity do the reverse.\textsuperscript{16,21,44,49,51,52,59} Since the early work of Wolff and Forbes\textsuperscript{68} showing dilatation of pial vessels with increased intracranial pressure, others have advanced the idea that the increased intracranial pressure seen in acute swelling actually results from vasodilatation due to a loss of vasomotor tone with resultant vessel engorgement.\textsuperscript{19,20,24,27} The increases in intracranial pressure brought on by the altered respiratory function will, of course, further compound these alterations.

Although the obvious treatment of this hypoxia, namely, oxygen administration, might be expected to improve the clinical situation in the late stages of head injury, these results draw attention to the possibility that it might in fact depress the hypoxic drive and even cause apnea. Although the data reported are drawn from animal experiments, the possibility that similar mechanisms may exist in the severely injured human must be considered. We believe that added oxygen should be given to patients showing this type of alteration in respiratory function only under close observation and with mechanical
ventilation readily available should apnea result. In view of the possible inapplicability of animal data to the human condition, and since this experimental model simulates only the epidural hematoma, no closer relationship to the clinical condition is presumed.

**Summary**

We have presented observations on respiratory changes, intracranial pressure, and blood gases during experimental compression in dogs. Our work shows an early progressive alteration in respiratory pattern as the intracranial pressure is increased by compression. At a late stage the sensitivity of the central chemoreceptors for CO₂ (pH) becomes depressed. The primary chemical drive thus becomes peripheral or hypoxic. This hypoxia, necessary for continued respiratory stimulation, itself leads to further increase in intracranial pressure by vasodilatation. Attempts to improve the hypoxia by administration of oxygen, without added mechanical respiratory support at this stage, deprives the animals of the only remaining chemical respiratory drive. The possibility that a similar mechanism would operate in the severely brain injured human should be considered.

**References**


34. NAEYE, R. L. Alveolar hypoventilation and cor pulmonale secondary to damage to the respiratory center. Am. J. Cardiol., 1961, 8:416–419.


