ELECTROENCEPHALOGRAPHIC ACTIVITY DURING VOLUNTARILY
CONTROLLED ALVEOLAR HYPERVENTILATION

BY

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SUMMARY

The following results were obtained from a series of investigations in which alveolar
hyperventilation was controlled within narrow limits. (1) Delta rhythm was not
directly related to alveolar ventilation, alveolar carbon dioxide tension or excretion of
carbon dioxide. The appearance of delta rhythm was not necessarily associated with
loss of consciousness. (2) Frontal alpha rhythm was apparently related to alveolar
ventilation volume, although insufficient evidence was available for statistical proof.
(3) It was considered that the cerebral effects of hyperventilation were due to hypoxia,
and subjects were found to vary considerably in sensitivity to such effects.

Although the adverse effects of hyperventilation on cerebral function were recognized by earlier
workers, more detailed investigation of cerebral activity was not possible until the discovery was
made that cerebral electrical activity could be recognized with the aid of the electroencephalo-
graph (e.e.g.). Berger (1934) then described the slow waves (delta rhythm) which have since been
accepted as the classical effect of hyperventilation on the e.e.g. Since that time electroencephalo-
graphy has been extensively utilized to elucidate the way in which hyperventilation affects the
function of the brain; and conversely, hyperventilation has been used to precipitate abnormal
rhythms in neurophysiological and clinical investiga-
tions. It was early appreciated that a standard
hyperventilation test was desirable and many
attempts have been made to impose comparable
conditions on the subjects of e.e.g. examinations,
notably by Davis and Wallace (1942) and by
Gibbs and his co-workers (Nims et al., 1940;
Gibbs et al., 1942). However, for several reasons,
control of alveolar ventilation was not achieved
by these workers and since that time many more
papers have been published in which no attempt
has been made to control alveolar ventilation,
despite the suspicion that the blood carbon
dioxide tension was an important factor in the
development of delta rhythm. As a result of this
it has not been possible to define the alveolar or
arterial carbon dioxide tension at which delta
rhythm may be expected. However, since with
the controlled alveolar hyperventilation technique
the rate of change of alveolar carbon dioxide
tension and of excretion of carbon dioxide can
be controlled (Stoddart, 1964), it was considered
that the relationship between carbon dioxide
excretion and delta rhythm could be clarified.

METHODS

Three fit male adults took part in this investiga-
tion. Their physical characteristics are given in
table I.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (yr)</th>
<th>Height (in)</th>
<th>Weight (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>37</td>
<td>66</td>
<td>145</td>
</tr>
<tr>
<td>B</td>
<td>28</td>
<td>70.5</td>
<td>180</td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>70.5</td>
<td>150</td>
</tr>
</tbody>
</table>

The hyperventilation circuit described in an
earlier paper (Stoddart, 1964) was used and after
10 minutes at rest each subject hyperventilated
twice at Va 29 l./min, 18 l./min and 10 l./min
for from 10 minutes at 29 l./min to 19 minutes
at 18 and 10 l./min. Control conditions were
achieved by making each subject hyperventilate
twice at VA 29 l./min when 1750 ml/min carbon dioxide was added to the inspired air to maintain the end-tidal carbon dioxide tension at the resting level. The end-tidal carbon dioxide concentration was measured at rest and throughout hyperventilation with a thermal conductivity meter and pen recorder. Earlier investigation indicated that the end-tidal-arterial carbon dioxide tension difference (±1 SE) was +0.69 ± 0.082 mm Hg, which suggested that end-tidal gas closely represented alveolar air (Stoddart, 1965). The readings were corrected with the regression equations previously derived (Stoddart, 1965) and converted to carbon dioxide tension (mm Hg) by multiplying by (PB−47), where PB was the ambient atmospheric pressure and 47 mm Hg was the saturated water vapour pressure at body temperature.

The expired air was collected in Douglas bags for the last 3-minute period at rest and throughout hyperventilation, when the Douglas bags were changed every minute for the first 4 minutes and every 3 minutes thereafter. The volume of expired air was measured with a water-sealed gasmeter and converted to STPD and BTPS. A sample was taken from each bag into tonometers and its carbon dioxide concentration determined by Lloyd Haldane analysis. Repeated analyses had to agree to 0.02 per cent.

The sequence in which the subjects hyperventilated at the different alveolar ventilation rates was randomized.

The electroencephalographic recording was made from four needle electrodes inserted into the scalp over the left cerebral hemisphere so that frontal, parietal and occipital records could be isolated. The output from the needle electrodes was amplified and recorded with a pen recorder.

Lead 2 of the e.c.g. was recorded on another channel of the pen recorder so that the pulse rate could be determined. Venous blood was taken immediately before and after each experiment for blood sugar analysis.

The e.e.g., e.c.g. and alveolar carbon dioxide tension were recorded on electromagnetic tape. This was to enable the e.e.g. to be analyzed with the aid of an analogue computer (Byford, 1965). The method is based on the separation electronically of the e.e.g. output into five frequency bands, in the 0–2, 2–4, 4–8, 8–16 and 16–32 c.p.s. range. The tape recordings are then transferred on to recording paper for analysis. Figure 1 shows a recording of e.e.g. activity as analyzed in this way. Changes in electrical activity in any frequency band are indicated by changes in the slope of the lines representing that band. Also included in figure 1 are the e.c.g. and alveolar carbon dioxide records during hyperventilation. These features are not clearly seen, as the record had to be reduced in size for reproduction.

RESULTS

Alveolar carbon dioxide tension and carbon dioxide excretion.

These values are given in figures 2 and 3 which represent those obtained in 27 experiments. Electroencephalographic activity was recorded in only 18 of these. The vertical bars in figure 2 represent ±2 SE. The standard errors about the mean volume of carbon dioxide excreted were:

- at VA 29 l./min, 18.72 ml;
- at VA 18 l./min, 12.08 ml;
- and at VA 10 l./min, 9.95 ml.

Electroencephalographic changes.

Delta rhythm. Delta rhythm was taken to be e.e.g. activity of less than 4 c.p.s. An attempt was made to relate the appearance of delta rhythm to the alveolar carbon dioxide tension and the volume of carbon dioxide removed from body stores. No delta rhythm was recognized during the control experiments nor during hyperventilation at VA=10 l./min with any subject and only sporadic delta rhythm was seen at VA=18 l./min. At VA=29 l./min subjects B and C showed delta rhythm during both experiments and subject A showed delta rhythm on one occasion. The times of onset of delta rhythm varied between subjects and between experiments (table II). Consequently, since the rate of change of alveolar carbon dioxide

<table>
<thead>
<tr>
<th>Subject</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Occipital</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>3.9</td>
<td>4.3</td>
<td>4.0</td>
</tr>
<tr>
<td>B</td>
<td>1.3</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>C</td>
<td>2.54</td>
<td>2.6</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td>3.6</td>
<td>3.6</td>
<td>3.54</td>
</tr>
</tbody>
</table>
Fig. 1
Recording of electroencephalographic activity as analyzed by separation of the output into five frequency bands. Upper traces are records of electrocardiogram and alveolar carbon dioxide tension.

Fig. 2
End-tidal carbon dioxide tension during hyperventilation (mean ± 2 SE).
tension and the rate of removal of carbon dioxide from body stores was within the limits shown in figures 2 and 3, the appearances of delta rhythm was not directly related to these factors.

**Alpha rhythm.** The description "alpha rhythm" is usually restricted to activity in the 8–16 c.p.s. range arising in the occipital area but the term will be used in this section for all rhythms of that frequency. Rhythms of alpha frequency from the frontal lobe were examined to determine if alpha activity was increased with hyperventilation and whether the increase was related to alveolar ventilation. Activity was determined from the slope of band 4 in the e.e.g. analyses (fig. 1) and the ratio of the slope during hyperventilation to that at rest was calculated. The results are given in table III. Insufficient information was available for statistical analysis but the results suggest that alpha rhythm was related to alveolar ventilation and excretion of carbon dioxide.

**Pulse rate during hyperventilation.**

The subjects' pulse rates were taken from the electrocardiograph. Table IV shows the pulse rates during the final minutes of the pre-hyperventilation rest periods, at three periods during hyperventilation, and during the first minute of the post-hyperventilation rest period. Statistical analysis showed that the pulse rates during the pre-hyperventilation rest period were not significantly different in any experiment but that thereafter the pulse rates were related to the alveolar ventilation (P<0.001–0.01). The pulse rate throughout the control experiments was significantly lower (P<0.001) than during hyperventilation at the comparable alveolar ventilation level.

**Blood sugar level and hyperventilation.**

Venous blood for blood sugar determination was withdrawn immediately before and after each experiment. The results are given in table V. Column 1 refers to the pre-hyperventilation and column 2 to the post-hyperventilation specimens. There was no significant difference between the blood sugar level of pre-and post-hyperventilation specimens of any subject. The levels for subject C were lower than those of the other two subjects but the level of significance (P<0.05) was doubtful.
TABLE III
Frontal alpha rhythm. Ratio of activity, as determined from the slope of band 4, during hyperventilation and at rest.

<table>
<thead>
<tr>
<th>Subject</th>
<th>29 l./min (isocapnic)</th>
<th>29 l./min</th>
<th>18 l./min</th>
<th>10 l./min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.25</td>
<td>2.40</td>
<td>1.33</td>
<td>1.66</td>
</tr>
<tr>
<td>B</td>
<td>0.85</td>
<td>2.5</td>
<td>2.42</td>
<td>2.0</td>
</tr>
<tr>
<td>C</td>
<td>0.83</td>
<td>4.5</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Mean</td>
<td>0.94</td>
<td>2.81</td>
<td>2.20</td>
<td>1.36</td>
</tr>
</tbody>
</table>

TABLE IV
Pulse rates during hyperventilation (beats/min).

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Subject</th>
<th>Resting</th>
<th>0–1</th>
<th>4–5</th>
<th>9–10</th>
<th>Resting</th>
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<tbody>
<tr>
<td>(a) Control</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>A</td>
<td>90</td>
<td>95</td>
<td>105</td>
<td>105</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>95</td>
<td>100</td>
<td>115</td>
<td>110</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>88</td>
<td>98</td>
<td>98</td>
<td>97</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>(b) VA=29 l./min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A</td>
<td>95</td>
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<td>130</td>
<td>120</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>90</td>
<td>115</td>
<td>130</td>
<td>125</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>130</td>
<td>120</td>
<td>110</td>
<td>85</td>
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</tr>
<tr>
<td>Mean</td>
<td>89</td>
<td>119</td>
<td>125</td>
<td>118</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>(c) VA=18 l./min</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A</td>
<td>95</td>
<td>95</td>
<td>115</td>
<td>105</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>90</td>
<td>90</td>
<td>105</td>
<td>100</td>
<td>90</td>
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</tr>
<tr>
<td>Mean</td>
<td>90</td>
<td>95</td>
<td>104</td>
<td>101</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>(d) VA=10 l./min</td>
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<td>A</td>
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<tr>
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<td>90</td>
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<td>90</td>
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</tr>
<tr>
<td>Mean</td>
<td>86</td>
<td>88</td>
<td>93</td>
<td>91</td>
<td>83</td>
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</tbody>
</table>
ELECTROENCEPHALOGRAPHIC ACTIVITY AND HYPERVERSALITATION

Table V

Venous blood sugar level (mg/100 ml) and hyperventilation. Pre-hyperventilation values in column 1 and post-hyperventilation values in column 2.

<table>
<thead>
<tr>
<th>Subject</th>
<th>V̇AV, l./min BTPS</th>
<th>29 (+CO₂)</th>
<th>29</th>
<th>19</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
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<td>1</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

DISCUSSION

Since delta rhythm was first reported during hyperventilation numerous investigators have attempted to relate the appearance of such rhythms to excretion of carbon dioxide from the body. Several theories of the causation of delta rhythm have been advanced. The most widely accepted theory is that hypocapnia reduces cerebral blood flow and results in reduced cerebral oxygenation (Davis and Wallace, 1941). An alternative theory, that of Nims and his co-workers (1940), is that delta activity is a function of defective cerebral vasoconstriction. They considered that vasoconstriction was a protective homeostatic mechanism which attempted to maintain the tissue carbon dioxide tension in the presence of hypocapnia and that only when vasoconstriction failed did delta rhythm appear. Another theory related the appearance of delta rhythm to changes in blood pressure and pulse rate during hyperventilation (Darrow and Pathman, 1943, 1944). These workers found that hyperventilation was accompanied by a fall in blood pressure and their investigations showed that if the subject's pulse rate rose simultaneously, delta rhythm appeared. They concluded that this indicated that the normal cerebral vasoconstrictive effect of vagal activity had failed.

Davis and Wallace (1942) stated that delta rhythm could be abolished by causing the subjects to breathe oxygen instead of air, which lent support to the anoxic theory. However, other investigators have been unable to confirm these findings (Fenn et al., 1949; Meyer and Waltz, 1960) and indirect estimations indicated that cerebral oxygen consumption was not reduced during hyperventilation (Kety and Schmidt, 1946, 1948). However, these workers did consider that mean cerebral oxygenation could be impaired due to the drop in venous oxygen content (mean 50 per cent) they observed. Cain (1962) showed that cerebral excess lactate production was not increased during hyperventilation which, he considered, indicated that cerebral oxygenation was adequate. He too observed a marked fall in the oxygen content of sagittal sinus blood.

It has also been suggested that hyperventilation-induced alkalosis and hypocapnia could shift the oxygen dissociation curve for haemoglobin, thus reducing the availability of oxygen (Carryer, 1947). If a standard oxygen dissociation curve is consulted, however, it may be seen that a shift in pH of from 7.4 to 7.6 due to respiratory alkalosis would not significantly affect the oxygen saturation of haemoglobin at Po₂ of from 100 to 80 mm Hg. On the other hand, venous oxygen saturation would increase more markedly as a result of the pH change. It is not yet possible to determine whether the arterial or venous oxygen tension more closely represents tissue tension. The concept of mean tissue tension as being the venous tension + A-V tension difference (Barcroft, 1934), although useful as a working principle, is not widely accepted. The Bohr calculation (Bohr, 1909) which is based on the assumption that each quantum of tissue removes an equal quantum of oxygen from the capillary blood is also open to criticism because it is founded on a concept of unidirectional flow through parallel capillaries (Thews, 1963).
counter-current flow may exist and the possibility of mass fluid movement between capillaries has been suggested (Discussion, Ciba Symposium, 1964). No satisfactory theoretical calculation can be thus derived to determine tissue oxygen tensions. Thews (1953, 1960) concluded that the oxygen tensions of brain grey matter were lower than previously assumed (of the order of 17 mm Hg) and that the effects of reduced oxygen supply would be observed whenever the oxygen tension was not sufficient for complete saturation of cytochrome oxidase; he suggested that if the venous oxygen tension fell by only 10 mm Hg, this could occur.

It is also considered that cellular metabolism may be adversely affected, despite apparently normal oxygen consumption, if the capillary oxygen tension falls below a critical value (Opitz, 1950). If the opinions of these workers are taken together with those of Kety and Schmidt (1946) it may be seen that hyperventilation could result in cerebral hypoxia. Gibbs, Davis and Lennox (1935) showed that hyperventilation, anoxia and ischaemia all produced similar changes in the e.e.g.

It is well known that hyperventilation hypocapnia results in cerebral vasoconstriction (Gibbs, Maxwell and Gibbs, 1947; Kety and Schmidt, 1946, 1948; Lewis et al., 1960) and it has also been shown that changes in blood hydrogen ion concentration cause alterations in cerebral blood flow and electroencephalographic activity only when accompanied by changes in arterial carbon dioxide tension (Schieve and Wilson, 1953; Swanson, Starney and Plum, 1958). Similarly Lambertsen and his co-workers (1961) showed that the cerebral circulation was controlled principally by the arterial carbon dioxide tension and that the hydrogen ion concentration played a very minor part. Forster (1964) concluded that the most important factor controlling cerebral oxygenation was the capillary blood volume per unit of tissue. However, the results of the present investigation into delta rhythm suggest that if this is due principally to hypoxia, the degree of vasoconstriction and the capillary blood flow are not directly related to the arterial carbon dioxide tension, and other factors, such as cardiac output, may be involved.

The relationship which was demonstrated between the incidence of frontal rhythm of alpha frequency and the alveolar ventilation is of interest. Byford and his co-workers (1966) exposed a group of subjects to graduated degrees of hypoxia in a decompression chamber. They found a close correlation between the appearance of frontal alpha rhythm and the level of hypoxia imposed. If these findings are accepted, the results of the present investigation may suggest that during hyperventilation, the degree of cerebral hypoxia is related to the alveolar ventilation and in turn to the alveolar carbon dioxide tension. These results would be expected if cerebral oxygenation was directly related to the arterial carbon dioxide tension and it may be that frontal alpha rhythm is a more direct indication of cerebral hypoxia than is delta rhythm. However, it must be emphasized that the relationship between alpha rhythm, hyperventilation and hypoxia is a presumptive one.

Additional information of interest was obtained from this part of the investigation. Subject B showed delta rhythm earlier than subject C but did not ever lose consciousness completely, and was able to continue to hyperventilate for the allotted time. On the other hand, subject C became unconscious and was unable to hyperventilate after from 5 to 7 minutes of hyperventilation at $V_A = 29$ l./min. Similarly, subject C became apnoeic and then grossly underventilated during the rest period following hyperventilation, during which time delta rhythm persisted. A similar observation was made by Lloyd-Smith (1950). This finding reinforces the hypothesis that delta rhythm was at least in part due to hypoxia, because during the apnoeic period carbon dioxide accumulation would be occurring and the arterial oxygen tension would be falling.

The blood sugar measurements were made because it is widely held that the level of circulating blood sugar is an important factor in determining the appearance of delta rhythm. It is considered that a high blood sugar level allows the brain tissue to function normally in the presence of hypoxia and hypocapnia (Davis and Wallace, 1941; Rubin and Turner, 1942; Brazier, Finesinger and Schwab, 1944). Davis (1941) showed that hypoglycaemia without hyperventilation could itself produce delta rhythm. The results of the present investigation showed that there was
no significant difference between the blood sugar levels of the three subjects, although subject C, who was most markedly affected by hyperventilation, had the lowest mean blood sugar level.

The observation that the subject's pulse rate was related to the alveolar ventilation may be associated with the fact that cardiac output rises with alveolar ventilation (Kety and Schmidt, 1948; Burnum, Hickam and McIntosh, 1954; Donevan et al., 1962; McGregor, Donevan and Anderson, 1962). The observation that the pulse rate increase during isocapnic hyperventilation was not so marked as that during hypocapnic hyperventilation at the same alveolar ventilation level is in agreement with the findings of McGregor, Donevan and Anderson (1962). These workers found that the cardiac output rose less during isocapnic than during hypocapnic hyperventilation. This in turn was partially explained by the results reported by Newhouse et al. (1964) who observed that less muscular work was done during isocapnic hyperventilation than during hypocapnic hyperventilation.

REFERENCES


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