POSTOPERATIVE HUMAN REACTION TIME AND HYPOCARBIA DURING ANAESTHESIA

BY
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SUMMARY
To study the effect of hypocarbia during anaesthesia on postoperative performance of a reaction time test, thirty-seven selected surgical patients were anaesthetized in a manner which does not alter cerebral blood flow at normal arterial Pco₂ levels. Patients were hyperventilated and variable amounts of carbon dioxide (0–2 per cent) were added to the inspired mixture to obtain a steady PaCO₂. A range of PaCO₂ of 12 to 38 mm Hg was obtained in the thirty-seven patients. In twenty patients whose PaCO₂ was below 24 mm Hg throughout the procedure there was postoperative prolongation of reaction time which lasted 3 to 6 days. Seventeen patients, whose PaCO₂ was greater than 24 mm Hg did not demonstrate this prolongation. There were no significant differences in age, sex, duration and type of procedure, anaesthetic dose, and levels of oxygenation in the two groups which could account for the observed results.

Since Kety and Schmidt (1946, 1948) demonstrated the prime role of arterial Pco₂ in the regulation of cerebral blood flow, there have been many studies of the effects of hyperventilation on the brain. Sugioka and Davis (1960) first suggested that hyperventilation is a possible cause of cerebral hypoxia. H. Wollman and colleagues (1965, 1968) have quantitated the diminution in cerebral blood flow associated with varying degrees of hypocarbia and found a 43 per cent fall in cerebral blood flow at an arterial Pco₂ of 19 mm Hg. In studies of cerebral venous lactate and pyruvate levels of these hyperventilated patients, Alexander and colleagues (1965, 1968) have concluded that anaerobic utilization of glucose was increased in severely hypocapnic subjects. Gotch and Meyer (1965) and Stoddart (1967) have documented electroencephalographic changes during hyperventilation which are similar to changes seen in mild hypoxia.

Attempts to evaluate the functional significance of these changes have been made by Allen and Morris (1962) and Whitwam and associates (1966) who used critical flicker fusion tests and arrived at conflicting interpretations. Robinson and Gray (1961) in evaluating the effects of hyperventilation on a variety of psychological tests and subjective clinical evaluations did not detect significant abnormalities. Their tests were representative of the complex functions of the brain but are not applicable for quantitative evaluation of subtle changes in these functions.

Reaction time has been used as an index of recovery from anaesthesia in the determination of “street fitness” after out-patient anaesthesia (Doenicke, Kugler and Laub, 1967). This test has been a useful tool in evaluation of disease states (Sutton and Zubin, 1965) and physiological changes (Harter, 1967).

The object of this study was to evaluate the alterations in cerebral function associated with varying degrees of hyperventilation using a parameter which can be measured with a reasonable degree of reliability and sensitivity, i.e. reaction time.

METHODS

Patient selection.
Thirty-seven informed and consenting patients, of both sexes, between the ages of 19 and 56, and scheduled for elective surgery, were the subjects of this study. The surgical procedures were superficial, restricted to areas either below the tenth

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thoracic segment, or the non-dominant upper extremity, and could be expected to require a postoperative hospitalization of at least 6 days. None of the patients showed evidence of anaemia, cardiovascular, neuropsychiatric or metabolic disorders. Patients who developed postoperative fever and those who required narcotics for pain were excluded from the analysis of data.

**Anaesthesia.**

All patients were medicated with pethidine 50–75 mg and hyoscine 0.4 mg given intramuscularly 1 hour prior to anaesthesia. Induction was accomplished with sodium thiopentone 4.5–6.0 mg/kg while the patient was breathing 100 per cent oxygen. Relaxation for intubation and maintenance was provided by tubocurarine 0.5–0.9 mg/kg. Anaesthesia was maintained with 70 per cent nitrous oxide, 30 per cent oxygen, at flow rates of at least 6 l./min. All patients were ventilated at approximately 2–3 times the ventilation predicted to be adequate by the Radford nomogram (1954). Ventilation was maintained by use of an Air Shields anaesthesia ventilator or a Takaoka ventilator. Randomly selected patients received carbon dioxide, 1 or 2 per cent, added to the inspired mixture and administered via a non-rebreathing system with the Takaoka ventilator. All patients received a constant inspired mixture throughout their anaesthetic. Within 10–15 minutes after induction of anaesthesia, a Riley needle was placed in a radial artery and intermittent samples were obtained and analysed with the appropriate electrode for $P_{CO_2}$, $P_{O_2}$, and pH. Since little variation in $P_{CO_2}$ was seen on random intermittent sampling, a value representative of the $P_{CO_2}$ during the anaesthetic was assigned to each patient. At the conclusion of the procedure all patients received atropine 1.6 mg and neostigmine 5.0 mg intravenously and were extubated when spontaneous ventilation and muscular activity were judged to be adequate.

The reaction time test.

The apparatus consisted of two series circuits with a patient's switch and an operator's switch (fig. 1). The light stimulus which was manually presented when the test administrator pressed his hidden switch produced a characteristic deflection on the e.c.g. recorder (Electronics for Medicine); the patient's response also produced a characteristic deflection. The interval between stimulus presentation and patient response could then be measured to 0.02 second. In our study stimuli were single light flashes. However, modifications of the stimulus circuit to allow the presentation of multiple stimuli and patterns could allow study of learning and memory in future studies. This "home-made" reaction time test apparatus is much simpler, more portable and considerably less expensive but less precise than commercially available reaction time (RT) equipment which can measure RT to 0.001 second and have rigidly standardized light stimuli and automated stimulus programmes. Therefore, the reliability of this apparatus was pre-tested on eighteen normal subjects who were hospital personnel. These subjects were tested daily for 7 days.

After an initial period of training, the patients were presented with stimuli at irregular randomly spaced intervals of 2–5 seconds. Each patient was studied on the pre-operative day as well as each postoperative day, where possible, for one week. The average of ten or more trials was accepted as the data for a specific day's run. Conditions for the test, such as position, time of day, lighting, exclusion from distractions, and instructions were similar in all subjects. Responses faster than 0.13 second were judged anticipations and were discarded (Sutton and Zubin, 1965) but all other data are included.

Data were analysed with Student's t test or Pearson's coefficient of correlation ($r$) where applicable.
RESULTS

Reliability of the test.

The data obtained from the eighteen subjects were analysed in order to determine the reliability of our test apparatus and procedure. Daily average reaction times for the group are represented in table I and demonstrate little change in group means with repetition of the test. The reaction times of the individuals for each day were analysed for correlation with all other days' results. Values of r which were obtained ranged from 0.81 ± 0.08 to 0.94 ± 0.03 (table II). This degree of correlation is considered more than adequate evidence of reliability for a test of cerebral function (Van Ommer and Williams, 1941).

Changes in reaction time with hypcapnia.

The per cent changes in reaction time (%ΔRT), for each postoperative day compared with pre-operative reaction times are presented in figures 2–5. These changes were plotted against

$$\text{Table I}
\begin{array}{lcccccc}
\text{Day} & 1 & 2 & 3 & 4 & 5 & 6 & 7 \\
\hline
\text{Mean} & 0.32 & 0.33 & 0.33 & 0.33 & 0.32 & 0.30 & 0.28 \\
\text{SD} & ±0.08 & ±0.08 & ±0.10 & ±0.11 & ±0.08 & ±0.08 & ±0.07 \\
\text{SEM} & ±0.02 & ±0.02 & ±0.02 & ±0.03 & ±0.02 & ±0.02 & \\
\end{array}
\text{Table II}
\begin{array}{lcccccc}
\text{Day} & 1 & 2 & 3 & 4 & 5 & 6 & 7 \\
\hline
1 & \text{—} & 0.88 ± 0.05 & 0.88 ± 0.05 & 0.88 ± 0.05 & 0.81 ± 0.08 & 0.89 ± 0.05 & 0.84 ± 0.07 \\
2 & \text{—} & 0.91 ± 0.04 & 0.84 ± 0.07 & 0.82 ± 0.08 & 0.83 ± 0.07 & 0.82 ± 0.08 & \\
3 & \text{—} & \text{—} & 0.93 ± 0.03 & 0.83 ± 0.07 & 0.87 ± 0.05 & 0.85 ± 0.07 & \\
4 & \text{—} & \text{—} & \text{—} & 0.86 ± 0.06 & 0.89 ± 0.05 & 0.84 ± 0.07 & \\
5 & \text{—} & \text{—} & \text{—} & \text{—} & 0.92 ± 0.04 & 0.84 ± 0.07 & \\
6 & \text{—} & \text{—} & \text{—} & \text{—} & \text{—} & 0.94 ± 0.03 & \\
\end{array}$
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18 22 34 38

Pre-operative v. Postoperative day 3. Per cent change of reaction time (% ART) with varying intra-operative Pco₂ levels.

14 18 22 26 30 34 38

Pre-operative v. Postoperative day 6. Per cent change of reaction time (% ART) with varying intra-operative Pco₂ levels.

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produced only minute changes in oxygen content, for no PaO₂ was below 86 mm Hg in either group, and all patients were alkalotic and therefore had increased oxygen saturation of haemoglobin at lower oxygen tensions.

When the daily mean reaction times of these two groups were compared (fig. 6) significant differences were seen on the first postoperative day (P<0.001), the second (P<0.001) and the third (P<0.01). As late as the sixth day a significant (P<0.05) difference was noted between the two groups.

**DISCUSSION**

H. Wollman and associates (1968) found that cerebral blood flow was diminished by 43 per cent at a PaCO₂ of 19 mm Hg. An additional 17 per cent fall in blood flow was seen at a PaCO₂ of 10 mm Hg. Wollman and associates (1965) showed that, at normal PaCO₂ levels, anaesthesia with thiopentone, 70 per cent nitrous oxide, and tubocurarine did not appreciably change cerebral blood flow. Therefore, if all patients receive the same form of anaesthesia and if Pco₂ levels are adjusted by changing inspired and hence arterial Pco₂, cerebral blood flow can be changed in a known way and the effects of these changes on a parameter of cerebral function can be studied. This presupposes a homogeneous population of patients with respect to age, absence of pre-existing significant diseases, type and duration of operative and post-operative stress. Identical premedication, anaesthetic and postoperative medications are mandatory. No other variables, such as anaemia, acidosis, hypotension, hyperthermia and hypoxia, should be present. Finally the parameter of cerebral function to be tested should be reliable and sensitive. We believe we have observed the above precautions and avoided these limiting factors (tables I–IV).

Although the possibility exists that a delay in reaction time can occur at any site in the nervous pathways, the most likely site for such delays is within the central nervous system, altered by decreased perfusion of the brain during hypocarbia. Hypocarbia and alkalosis have also been postulated as an aetiological mechanism for tissue hypoxia and metabolic acidosis outside the central nervous system (Papadopoulos and Keats, 1959), but those changes were mild and not progressive with increasing duration of hyperventilation (Dobkin, Byles and Neville, 1966).

In our study, responses to light stimuli were consistent with published reports of human reaction time (Harter, 1967; Sutton and Zubin, 1965) despite the simplicity of our apparatus. Harter (1967) has shown that the inhalation of up to 3.5 per cent carbon dioxide by conscious subjects decreased human reaction time. Above this level reaction time was prolonged and the subjects were narcotized. These changes of reaction times were shown to correlate with the alpha rhythm of the electroencephalogram.

We found a significant prolongation of reaction times in patients in whom the PaCO₂ was below 24 mm Hg when compared with their own pre-operative reaction times (P<0.005) and to identically treated patients in whom the PaCO₂ was above 24 mm Hg (P<0.001). These findings are consistent with alterations in critical flicker fusion reported by Allen and Morris (1962), as well as the fall in cerebral blood flow measured by Wollman and associates (1968). The alterations in reaction times lasted at least 3 days but were
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present as long as 6 days in some patients. This is consistent with the duration of abnormality in critical flicker fusion found by Allen and Morris (1962) in a study which was less rigidly controlled and documented with respect to the variables previously mentioned. That the results are in variance with the rigidly controlled experiment and findings of Whitwam and associates (1966) is not surprising although not easily explained. The $P_{vco_2}$ values reported by them indicate $Pa_{co_2}$ values which fall around or below the critical level of 24 mm Hg found in the anaesthetized patient. Obviously, the patients in this study represented an entirely different sample from the six young healthy subjects in Whitwam's group. Their failure, therefore, to find cerebral functional changes immediately after hyperventilation does not rule out the possibility that transient or reversible changes may be found in the hospitalized patient subjected to surgery, anaesthesia, hyperventilation and a multitude of drugs. The authors stated, "there are many factors in the anaesthetized patient other than $Pa_{co_2}$ and systemic blood pressure which may influence haemodynamics and produce changes in cerebral function."

It is concluded that severe hypocarbia during anaesthesia is associated with a prolonged reaction time for at least 3–6 days post-hyperventilation. This change in reaction time was associated with relatively short periods of hyperventilation (103 ± 51 minutes) in relatively young people (33 ± 11 years). Patients with advanced age, arteriosclerosis, hyperthermia, and those in whom anaesthesia was prolonged, were excluded from this study. These factors could be expected to exaggerate the unfavourable cerebral response to hypocarbia.

REFERENCES


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LE TEMPS DE REACTION DE L'HOMME ET L'HYPOCARBOXEMIE PENDANT L'ANESTHESIE

SOMMAIRE

Pour étudier l'effet de l'hypocarboxémie pendant l'anesthésie sur l'exécution d'un test de réaction post-opératoire, 37 malades chirurgicaux ont été anesthésiés d'une façon qui n'altère pas le flux sanguin cérébral pour des taux normaux de Pco₂. Les malades étaient hyperventilés et des doses variables de CO₂ (0-2 pourcents) ont été ajoutées au mélange inspiré pour obtenir une Paco₂ constante. Un taux de Paco₂ de 12 à 38 mm Hg a été obtenu chez ces 37 malades. Chez 20 malades dont la Paco₂ était en-dessous de 24 mm Hg pendant l'opération on a remarqué un retard de réaction postopératoire qui durait de 3 à 6 jours. Dix-sept malades dont la Paco₂ était plus grand que 24 mm Hg ne présentaient pas de tel retard. Il n'y avait pas de différences significatives quant à l'âge, le sexe, la durée ou le type de l'intervention, la dose des anesthésiques et le niveau d'oxygénation dans les deux groupes qui pourraient expliquer les résultats observés.

BOOK REVIEW


This small Swiss book is of outstanding quality. The writer, who is director of the department of surgical research at Bern, has given an intensely practical and up-to-date account of the use of antibiotics in surgery. In the first five chapters the physiological and pathological basis of the interaction of the body and various bacteria are described in detail and the biological action of some twenty-five antibiotics is discussed. These subjects which many surgeons and anaesthetists find difficult to understand are here dealt with in clarity and brevity unusual in German medical literature.

In the next two chapters the basic factors of hospital infections, their causes, prevention and management, are described in detail. For the practising surgeon and anaesthetist these chapters are a mine of information.

Finally, six chapters are devoted to discussion of antibiotic therapy for specific conditions. Antibiotic resistance, therapy using a combination of antibiotics, and complications of antibiotic therapy, are all described in considerable detail before the various surgical conditions and their antibiotic treatment are outlined.

A very full and up-to-date bibliography of some 650 references is included in this volume.

The author has to be congratulated on writing such a readable treatise on a subject which has become of prime importance for all doctors working in the surgical wards of hospitals. It is a great pity that because the book is written in German it will not be freely read by English-speaking medical men and it would be highly desirable if the book could be translated into English.

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ERRATUM

In the paper entitled "A double-blind controlled study of the effects on respiration of pentazocine, pheneridine and morphine in normal man" appearing on page 864 of the November 1968 number, Dr. J. Barker's initials were inadvertently given as J. G.