Arterial PaO$_2$ and PaCO$_2$ influence seizure duration in dogs receiving electro-convulsive therapy

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The influence of arterial O$_2$ and CO$_2$ tensions on electroconvulsive seizure duration was investigated in five mongrel dogs under consistent anaesthetic conditions. Seizure durations were measured in a randomized protocol of nine possible combinations of arterial gas tension spanning increased, normal or decreased levels of PaO$_2$ and PaCO$_2$. Seizure duration was directly related to PaO$_2$ (p < 0.00001) and inversely related to PaCO$_2$ (p < 0.0001). A significant synergism was evident at the extremes of PaO$_2$ and PaCO$_2$, with seizure duration being greater than predicted for hyperoxia–hypocapnia and hypoxia–hypercapnia and shorter than predicted for hypoxia–hypocapnia and hyperoxia–hypercapnia. We conclude that arterial gas tensions strongly influence ECT-induced seizure duration and through this may influence the therapeutic efficacy of electroconvulsive therapy.

Anaesthesia for electroconvulsive therapy (ECT) has evolved from the use of nothing but physical restraint to a regimen of preoxygenation, a short-acting intravenous anaesthetic and a muscle relaxant, plus ventilation with a high inspired oxygen fraction immediately prior to and following the seizure-inducing stimulus. The anaesthetic agents have varied considerably, with emphasis being on rapid return of self-protective reflexes and minimization of potentially hazardous fluctuations in blood pressure or cardiac rhythm.

Key words

However, the therapeutic efficacy of ECT requires that the induced seizure be generalized[1] and of adequate duration. Although the exact relationship between ECT efficacy and cumulative seizure duration[2–5] remains controversial, there is general agreement that the desired anti-depressant effect is diminished when seizure duration is short. In this context, the use of anticonvulsants (i.e., intravenous induction agents) during ECT may be counterproductive. Many recent studies have probed the relationship of anaesthetic agent to seizure duration and found significant differences in seizure duration among otherwise anaesthetically acceptable regimens.[6–12] Unfortunately, many of these studies failed to control a fundamental variable that underlies all anaesthetic techniques, namely the patients' blood gas tension status during the seizure.

In the 1950's, Holmberg[13] noted the risk of hypoxaemia during ECT while Dahlberg-Parrow[14] reported that hypoxaemia and hypercapnia each separately reduced electrically induced seizure duration. More recently, it has been shown that seizures are prolonged when hyperoxic patients receiving ECT are hyperventilated to an end-tidal CO$_2$ level of two per cent. Before one can factor out the influences of specific anaesthetic agents, one must first establish the nature and extent of PaCO$_2$ and PaO$_2$ influence on seizure duration. Therefore we designed this study to assess systematically the interrelationships of arterial gas tensions and seizure duration. An animal model was developed because it permitted multiple measurements under standardized conditions, extending over a wide range of blood gas tensions.

Methods

Five male dogs weighing 18 to 24 kg were studied using a protocol approved by our university ethics committee. The dogs were prepared by having both carotid arteries externalized in skin loops under general anaesthesia. The loops were allowed to heal for a six-week period. On study days, each dog was anaesthetized with thiopentone (8–10 mg·kg^{-1}), paralyzed with gallamine (2 mg·kg^{-1}),
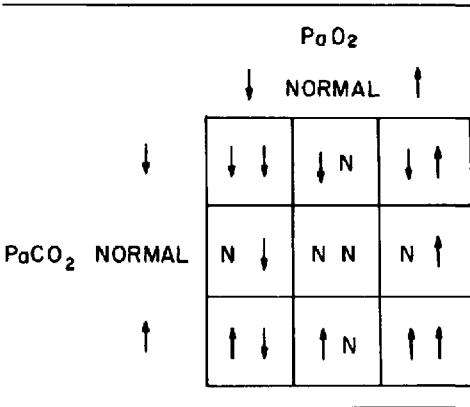
FIGURE 1   Diagram of the nine PaO_2 and $PaCO_2$ combinations that were evaluated in a randomized sequence for each dog.

intubated and ventilated using a Harvard Respiration Pump. Supplemental doses of thiopentone and gallamine were given over the course of the day, to maintain a basal level of anaesthesia and paralysis. A two-lead electroencephalogram, obtained using percutaneous electrodes in the F3-01 and F4-02 positions connected to a Grass Model 7 Polygraph EEG machine, was used to measure seizure duration. Two stimulating electrodes were applied to shaved temporal areas bilaterally. The stimulus to these electrodes was a 50 Hertz sine wave current of one second duration which was variable voltage, the latter being adjusted by a Variac Autotransformer. The voltage and current levels of each stimulus were measured using a Tektronix Type 502A Dual Beam Oscilloscope. A #20-guage teflon catheter was introduced percutaneously into one of the externalized carotid artery loops and this was flushed continuously using 0.9 per cent saline with heparin (1 u·ml^{-1}). Arterial blood taken from this line was analyzed for PaO_2 and $PaCO_2$ in triplicate using a Corning pH/Blood Gas Analyzer 165/2 calibrated with certified gas mixtures. Normothermia, as verified using a rectal temperature probe, was maintained with supplemental heating.

The PaO_2 and $PaCO_2$ were varied by mixing oxygen, air, nitrogen and carbon dioxide appropriately for low, normal and high levels of PaO_2 and normal and high levels of $PaCO_2$. Ventilator rate was increased to achieve hyperventilation. Nine different possible combinations were explored in this study as depicted in Figure 1.

The range used for hypoxia was 3.3–6.0 kPa (25–45 mmHg), for hyperoxia 53–67 kPa (400–500 mmHg), for hypocapnia 2.7–4.0 kPa (20–30 mmHg) and for hypercapnia 6.7–8.0 kPa (50–60 mmHg). The end-tidal CO_2

was monitored using a Beckman LB-2 Medical Gas Analyzer.

Preliminary trials were carried out on three separate days with each animal to find the supramaximal stimulating current and to assess the reproducibility of seizure duration at normoxia and normocapnia when given at 0.5-hour intervals over a 3.5-hour period. Each dog was then studied twice at the nine possible combinations of PaO_2 and $PaCO_2$ over three days in a preset randomized protocol. Protocols for each dog were recommended by our statistical consultants and were such that no set of conditions was repeated on the same day. All five dogs had separate and different protocols. The following sequence was used: five minutes prior to stimulus delivery, gas flows and ventilator settings were adjusted to achieve the desired arterial gas tensions. One minute before each stimulus thiopentone 1.5 mg·kg^{-1} was given intravenously. An arterial blood gas sample was drawn immediately before the stimulus. Following termination of the seizure, normoxia and normocapnia were restored. The dogs received six stimuli at ½ hour intervals on each study day with one week elapsing between study days.

In one dog, blood for thiopentone determinations was drawn immediately before each stimulus on all three study days. All samples were stored and analyzed by the chemistry laboratory using diphenylcarbazone-barbiturate spectrophotometric analysis on a single day.[13] Known reference standards were mixed on the day of measurement. The intra-assay variance of the analysis was ±5 per cent.

Results were analyzed using a computerized two-way multifactorial analysis of variance in conjunction with the Queen's University Department of Statistics. Multiple linear regressions were performed on data exhibiting significant F values. The computer program was Minitab* release 82.1.

Results

In the preliminary runs, seizure duration was found to be reproducible at 0.5-hour intervals. The mean coefficient of variation for repeated measures of seizure duration under conditions of normoxia and normocapnia was 5.1 per cent. With all dogs, no trend towards shortening or lengthening of seizure duration was noted over the day.

Mean thiopentone levels were 71.1 ± 5.7 (mean ± SD) mM·ml^{-1} for all three days with all values being within the limits of the error of the measurement. No discernable trend in the levels occurred over the course of any day.
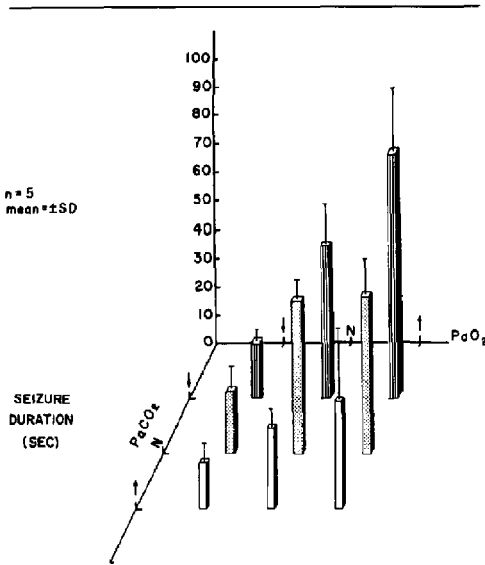
FIGURE 2 Three dimensional plot of seizure duration vs both PaO$_2$ and PaCO$_2$. The striped bars represent values obtained during hypocapnia plus low, normal or high arterial oxygen tension; the open bars indicate results for hypercapnia over the range of arterial oxygen tensions. The shortest seizures occurred in the presence of hypoxia plus hypercapnia; the longest seizures during hyperoxia plus hypocapnia.

The thiopentone levels after the first stimulus did not differ systematically from subsequent values confirming that the initial induction dose had been redistributed and/or metabolized by that time.

The Table gives the mean seizure duration with the standard deviations for the nine possible combinations of blood gases. These are shown graphically in Figure 2.

The statistical analysis confirmed that changing oxygen levels strongly affected seizure duration (p < 0.00001) with the seizure duration being directly related to the arterial oxygen level.

Seizure duration was inversely related to the arterial CO$_2$ level (p < 0.0001). A significant interaction between

TABLE Mean seizure durations (seconds) for each combination of PaO$_2$ and PaCO$_2$ (mean ± SD)

PaCO$_2$	PaO$_2$		
	↓	N	↑
↓	21.1 ± 3.9	54.7 ± 14.0	85.8 ± 23.1
N	23.0 ± 9.1	55.2 ± 8.2	57.0 ± 13.4
↑	17.1 ± 7.6	29.2 ± 7.0	39.7 ± 26.9

PaO$_2$ and PaCO$_2$ were evident (p < 0.001), indicating a synergism between these two. What was found was an increase in seizure duration for hyperoxia–hypocapnia and hypoxia–hypercapnia and a decrease in seizure duration for hypoxia–hypocapnia and hyperoxia–hypercapnia from the changes predicted by the linear regression coefficients for PaO$_2$ and PaCO$_2$ at these conditions. Although the factor for interanimal variance was large, it fell just short of significance in this study (p = 0.06).

Discussion

In this protocol, we attempted to reproduce significant clinical aspects of ECT under conditions in which arterial gas tensions could be controlled. Although there are numerous reports of how one or two changes in arterial blood gas tensions affect seizure durations[2–4,11,12,14–16] these have occurred in various types of animal models and humans using different methods to induce seizures with different lengths of blood gas alterations under multiple anaesthetic regimens. We systematically studied different combinations of PaO$_2$ and PaCO$_2$ in dogs under constant anaesthetic conditions. While some of these conditions might hopefully never be seen clinically, this approach allowed us to separate the effects of PaO$_2$ and PaCO$_2$ on seizure duration.

Repeated seizures during the same day theoretically might affect seizure duration but in the preliminary test periods, all five dogs exhibited no trends in seizure duration over the course of a day and there was no difference in seizure durations on different days under constant conditions of PaO$_2$ and PaCO$_2$. The randomization of PaO$_2$ and PaCO$_2$ combinations in each study represents an additional precaution taken to eliminate any possible influence of experimental sequence on seizure durations.

The supplemental dose of thiopentone used is similar to the smallest dose that would be used at our hospital (1.5 mg·kg^{-1}) for ECT. The dogs were kept lightly anaesthetized throughout the day by these intermittent supplements after the initial induction dose of 8–10 mg·kg^{-1}. This was done for ethical reasons so that the dogs would never be awake but paralyzed. It proved necessary to anaesthetize and paralyze the dogs in order to achieve the desired number of stimuli in one day. We found it impractical to allow the dogs to wake up between seizures in part because animal movements induced technical problems with the equipment, and in part because no really short-acting muscle relaxant exists for dogs (they do not hydrolyze succinylcholine rapidly).

The decision to adjust ventilator settings and gas composition five minutes before each stimulus was a compromise between mimicking the rapidly changing

conditions that occur in clinical ECT and our need for control and stability in the arterial blood gases. Further small changes in the arterial blood gases would occur should the settings be maintained, but the majority of the change will have occurred within five minutes.

Although the interanimal variance fell just short of significance, many of the individual data points exhibited marked variation, particularly during hyperoxic conditions. This variance was taken into account by the statistical analysis used.

Figure 2 best illustrates the effects of the various combinations of PaO_2 and $PaCO_2$. PaO_2 exhibited the most powerful influence on seizure duration. Hypoxia shortened seizure duration by $\frac{1}{3}$ to $\frac{1}{2}$ of that for normoxia regardless of the CO_2 level. This is compatible with work done in the 1940's and 50's which showed that anoxia abolishes seizures in animals.[15,16] It may be that decreased energy production caused by hypoxia during a period of very high energy expenditure or an increase in the waste products of anaerobic metabolism affect the cell's ability to function rapidly enough to meet the demands being made on it. It has been shown in animals and humans undergoing seizures that autoregulation is suspended[17–19] and that cerebral blood flow increases up to 260 per cent. In view of this, excess products of metabolism should be rapidly washed out and indeed Posner *et al.*[19] have shown that paralyzed, ventilated patients receiving ECT have only a modest rise in cerebral lactate levels. Therefore, inadequate energy production due to hypoxia would appear to be the likelier cause of shortened seizure durations.

This being true, then hyperoxia might be expected to prolong seizure duration, as was found in these experiments. Seizure duration was significantly prolonged by hyperoxia at all three $PaCO_2$ levels. This finding is consistent with previous studies.[2,11,12,14] It has been shown that animals paralyzed and ventilated with 30 per cent O_2 have adequate global oxygen delivery.[17] However, there is some controversy as to whether regional oxygen deficits occur.[20] If regional O_2 delivery is inadequate during normoxia, hyperoxia might improve on this, even though oxygen content is only increased by $2 \, ml \cdot 100 \, ml^{-1}$ blood when one goes from normoxia to hyperoxia.

Arterial CO_2 levels were inversely related to seizure duration but the effect was much less dramatic than that induced by changes in oxygen tension. The primary effect was noted with hypercapnia, which shortened seizure duration. Using an analysis of variance, a significant ($p < 0.0001$) negative linear relationship was found between seizure duration and $PaCO_2$. Since the effect of changes in $PaCO_2$ on CBF is suspended during a seizure, there must be some other explanation. CO_2 rapidly

crosses the cell membranes and it may be it affects seizure duration by altering intracellular pH, thus causing changes in the cell metabolism. During hypercapnia plus a seizure intracellular pH would be reduced on both respiratory and metabolic bases; during a hypocapnic seizure, the respiratory alkalosis would moderate the buildup of acid products in the neurons. Extreme changes in pH might interfere with cell functions so neurons would be unable to repolarize rapidly enough to maintain a seizure state. It would be of interest to investigate the effect of hypercapnia further in an animal model in which status epilepticus or spontaneous seizures occur, to see if such seizures could be shortened by deliberate administration of CO_2. Obviously before such a method could be used in humans, the mechanism of any such action would have to be delineated since it might prove toxic to neurons.

The synergism between PaO_2 and $PaCO_2$ is of interest. For unlike conditions of PaO_2 and $PaCO_2$ (e.g., hyperoxia–hypocapnia, and hypoxia–hypercapnia), there is an increase in observed seizure duration beyond the predicted additive effects of changes in PaO_2 and $PaCO_2$ alone. For like conditions (e.g., hyperoxia–hypercapnia and hypoxia–hypocapnia) there is a decrease in seizure duration from that expected from the changes in PaO_2 and $PaCO_2$ alone. Hyperventilation with high oxygen flows was shown by Bergsholm *et al.*[12] to prolong the seizure duration and in this study the longest durations occurred under these conditions (see Figure 2). Although the seizure durations observed during hypoxia and hypercapnia exceeded the value predicted from the individual linear regression lines for PaO_2 and $PaCO_2$, nonetheless the shortest seizures encountered occurred with this combination of blood gas tensions. It is almost as if a self-limiting protective mechanism exists naturally to terminate spontaneous seizures since during grand mal seizures people become apnoeic and rapidly become hypoxic and hypercapnic.

In summary, a subject's arterial blood gases significantly influence seizure duration. Changes in PaO_2 are directly proportional to changes in seizure duration with a significant shortening occurring during hypoxia. $PaCO_2$ exerts a weaker effect than PaO_2 being inversely related to seizure duration with a shortening of seizure duration occurring with hypercapnia. A synergistic effect occurs at the extreme conditions such that the longest seizures occurred with hyperoxia and hypocapnia. If cumulative seizure duration does turn out to be the best predictor of antidepressant efficacy, then the deliberate use of hyperoxia and hyperventilation to prolong individual seizures could reduce the total number of times that ECT would need to be administered to a patient.

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Résumé

On a examiné l'influence de pression artérielle de O_2 et de CO_2 sur la durée des convulsions produites par sismothérapie, chez cinq chiens bâtards dans des conditions anesthésiques identiques. Afin de mesurer les durées de convulsions, on a utilisé un protocole aléatoire de neuf combinaisons possibles de la pression artérielle du gaz s'étendant à des niveaux de PaO_2 et de $PaCO_2$ élevés, normaux, ou diminués. La durée de convulsions était directement reliée à la PaO_2 ($p < 0.00001$) et inversement reliée à la $PaCO_2$ ($p < 0.0001$). Un synergisme significatif se manifestait aux extrêmes de la PaO_2 et de la $PaCO_2$, accompagné d'une durée de convulsions plus élevée que prévu pour l'hyperoxie–hypocapnie et l'hypoxie–hypercapnie et plus courte que prévu pour l'hypoxie–hypocapnie et hyperoxie–hypercapnie. Nous concluons que les pressions artérielles du gaz influencent grandement la durée de convulsions induites par sismothérapie et peuvent ainsi influencer l'efficacité thérapeutique de la sismothérapie.