# SPECTRAL ANALYSIS OF THE EEG DURING HALOTHANE ANAESTHESIA: INPUT–OUTPUT RELATIONS

F. H. LOPES DA SILVA, N. TY SMITH[1], A. ZWART AND W. W. NICHOLS

*Brain Research and Cardio-vascular Physics Departments, Institute of Medical Physics TNO, National Health Research Organization, Utrecht (The Netherlands) and Department of Anesthesia, Stanford University Medical Center, Stanford, California (U.S.A.)*

This study was performed to extract parameters from the EEG which would give quantitative information about brain function during Halothane anaesthesia. Most studies concerning EEG changes during Halothane anaesthesia have been restricted to qualitative descriptions, for example those of Backman *et al.* (1964) and Barry Prynn and Redding (1968). Findeiss *et al.* (1969) suggested that frequency analysis was a useful method to establish quantitative relations between Halothane concentration and the EEG. However, in their studies the relationship between Halothane concentration and EEG spectrum was investigated in a static way, *i.e.*, the EEG spectrum was determined at steady concentrations of Halothane. In this study our aim was to determine the *dynamics* of the "Halothane-brain compartment" system, *i.e.*, to measure the response of the system to changes of its input as a function of time. As output we used the EEG spectrum. The Halothane input was changed by step and sinusoidal functions. Determining the dynamics of the system has a practical interest because the feasibility of using the EEG in a monitoring system for Halothane anaesthesia depends to a large extent on knowledge of the system's time constants. The system was also investigated at steady concentrations of Halothane. The results obtained in this study are also being used to improve a model of the distribution of Halothane in the body, which was reported by Zwart *et al.* (1972).

[1] Present address: Department of Anesthesia, University Hospital of San Diego County, 225 West Dickenson Street, San Diego, Calif. 92103, U.S.A.

## METHODS AND MATERIAL

### a. *EEG recording*

Five dogs (2 German boxers and 3 mongrels) were used. Two had implanted electrodes, either stainless-steel pins (1 mm diameter) placed in the skull down to the inner table or stainless-steel strands of wires (100 $\mu$ diameter, insulated to 1 mm from the tip) in several brain regions. In the other three dogs, the EEG was recorded from hypodermic needles placed in the scalp. The derivations which were selected for analysis in the former dogs were occipital-central and in the latter, from one needle placed at the inion lateral to the midline and another at the coronal suture of the same side. The EEG was amplified and transmitted by a 16-channel EEG radio-telemetering system (Storm van Leeuwen and Kamp 1969).

### b. *EEG analysis*

The EEG was analysed by a hybrid spectral analyser, consisting of a bank of 20 electronic bandpass filters covering the frequency range 2–32 c/sec, as described previously (Lopes da Silva and Kamp 1969). The frequency spectrogram could be continuously displayed on an oscilloscope screen so that an on-line form of analysis was possible. In addition, to obtain integrated quantitative information about the frequency spectrum, the running averages of the filter outputs were fed to a Computer of Average Transients (CAT 400 bTMC) so that the output amplitude of each filter was summed in the respective computer address for a chosen inter-

val of time. In the present study, the typical analysis epoch was 60 sec. Average spectral amplitude histograms are shown in Fig. 2. As a check on the analogue frequency analysis, a spectral analysis of some epochs was performed off-line on a digital computer (PDP-9) using the Fast Fourier Transform procedure. The results were essentially the same and only the former method is reported here.

c. *Anaesthetic procedure*

Anaesthesia was induced by a mixture of 20% $O_2$ and 80% $N_2O$ applied with a nose mask. After about 5 min the $N_2O$–$O_2$ mixture was changed to a mixture of $O_2$ and Halothane. As soon as the anaesthesia was deep enough the dog was intubated and attached to a fixed volume respirator (Palmer) in a non-rebreathing system. In a Forreger Copper Kettle, $O_2$ was saturated with Halothane (33% at 20.5°C). The desired concentration of Halothane in the inspired gas mixture was obtained by controlling the flow of the Halothane–$O_2$ mixture which was added to a constant flow of $O_2$ of 5 1/min. The flow was controlled by a specially designed electro-

mechanical valve which released a constant volume of $O_2$ (0.08 ml at 1 Atm) for every electrical pulse it received. The repetition rate of the pulses could be modulated between 0 and 100 pulses/sec following any function of interest (steps, sine waves), using a Wavetek generator. The ventilation was kept constant unless otherwise specified. The tidal volume was 14 ml/kg weight and the normal ventilation rate was 12/min.

The concentration of Halothane was changed in either a step or a sinusoidal pattern. End-expired Halothane was increased, or decreased, in steps of at least 0.5%, that is, the concentration was changed suddenly to another level and maintained at that level for a long period. Alternatively, inspired concentration was modulated in a sinusoidal fashion, with a mean concentration of 1.75% and peak-to-peak concentrations of 0.5 and 3.0%. The following parameters were measured: end-expired Halothane concentration, measured with an infra-red analyser (Hartmann and Braun); $P_aCO_2$, $P_aO_2$ and pH, which were measured by the Astrup method; end-expired carbon dioxide, $PCO_2$, was moni-
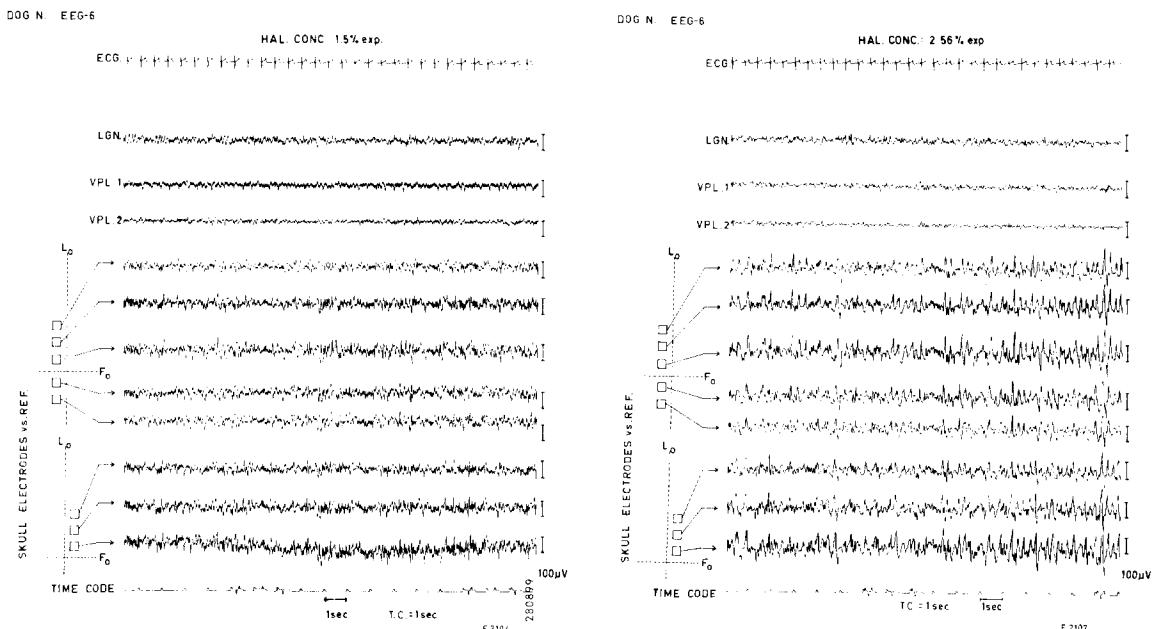


Fig. 1. EEGs recorded at two levels of Halothane concentration in expired air: 1.5 and 2.56%. EEGs from LGN (lateral geniculate nucleus), VPL 1 and 2 (two ventro-postero-lateral nucleus sites) and from 8 epidural skull electrodes (the positions of which in relation to the midline, $L_0$, and to the stereotaxic zero frontal plane, $F_0$, are indicated). The records are against a common frontal reference electrode. The first trace is the ECG. Note the increase in slow waves of large amplitude in the case of 2.56% expired Halothane. The change is most pronounced in cortical records.

tored by a Capnograph (Godart) in one dog; aortic pressure, measured by an 18-gauge central arterial pressure catheter (Sorenson) and a Statham P23Db pressure transducer; the electro-cardiogram in a conventional way; ascending aortic blood flow and left ventricular pressure were also measured in two dogs.

The cardiovascular parameters investigated will be the subject of a separate publication.

RESULTS

The quantitative studies reported here were always preceded by a qualitative evaluation of the EEG patterns. As regards the EEG changes during Halothane anaesthesia, no significant differences were found between superficial and subdural recordings. Fig. 1 illustrates some of these typical patterns. The same sequence of patterns was found invariably in all dogs. At the mean level of sinusoidal modulation, 1.75%, the characteristic EEG pattern was dominated by components at 4–8 c/sec. In contrast, at much lower Halothane concentrations (< 0.7%) the EEG was characterized by widespread activity at about 20 c/sec. At higher concentrations (>

2.5%) the EEG was typically of low frequency (2–3 c/sec) with occasional large amplitude bursts (200 $\mu$V in scalp recordings). At very high concentration (>4%) there was a gradual decrease of EEG amplitude with periods during which it was at the noise level.

a. *Step functions*

Step changes in Halothane concentration of 0.5% were easily detected as variations in the intensity of EEG spectral components (Fig. 3). The different components did not respond in an identical way to a step change. Their response was conditioned by the initial level of Halothane concentration in the inspired air, so that when
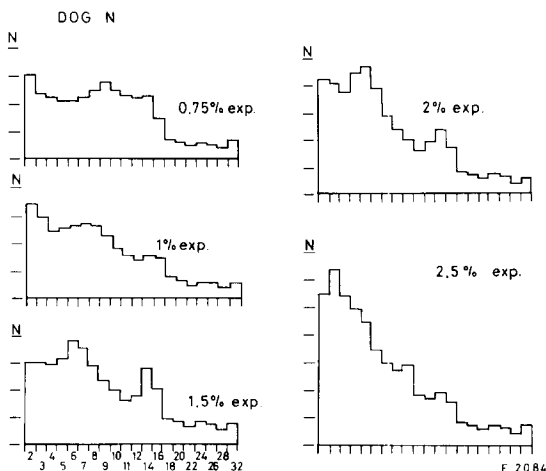


Fig. 2. EEG integrated frequency spectra obtained at different levels of Halothane concentration (% expired air) in equilibrium. Each spectrum results from the integration of one minute of EEG. The abscissa is frequency in c/sec. The ordinate is a spectral intensity scale in arbitrary units. Note that at increasing concentrations of Halothane the spectral intensity changes in absolute value (especially at frequencies < 8 c/sec) and also relatively (shift of average and peak frequency to the left).
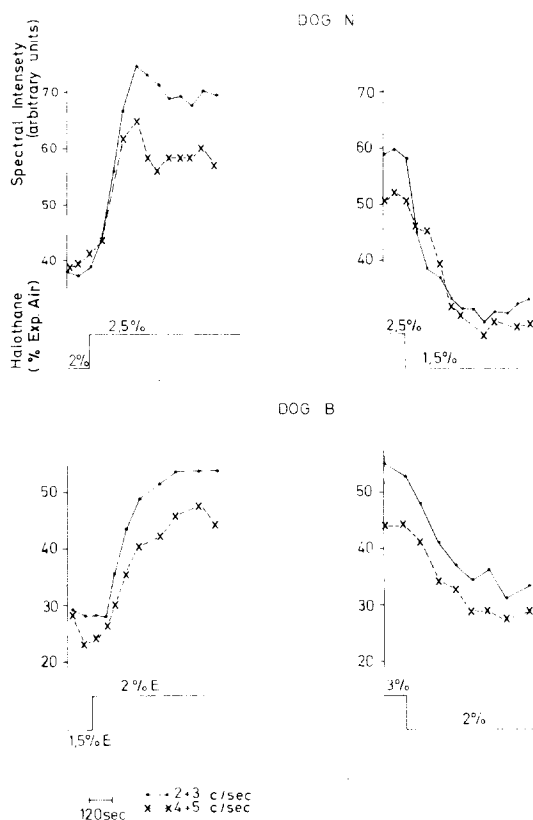
Fig. 3. EEG spectral responses to step changes in Halothane concentration for two dogs. Each of the four sets shows the response of the average of components 2 and 3 c/sec and 4 and 5 c/sec simultaneously with the step in Halothane concentration (% expired air). Note the similarity in rise time of the responses to steps in the positive and negative directions. Drift in spectral intensities can be noted because of different values of the spectral components at the same Halothane concentration.
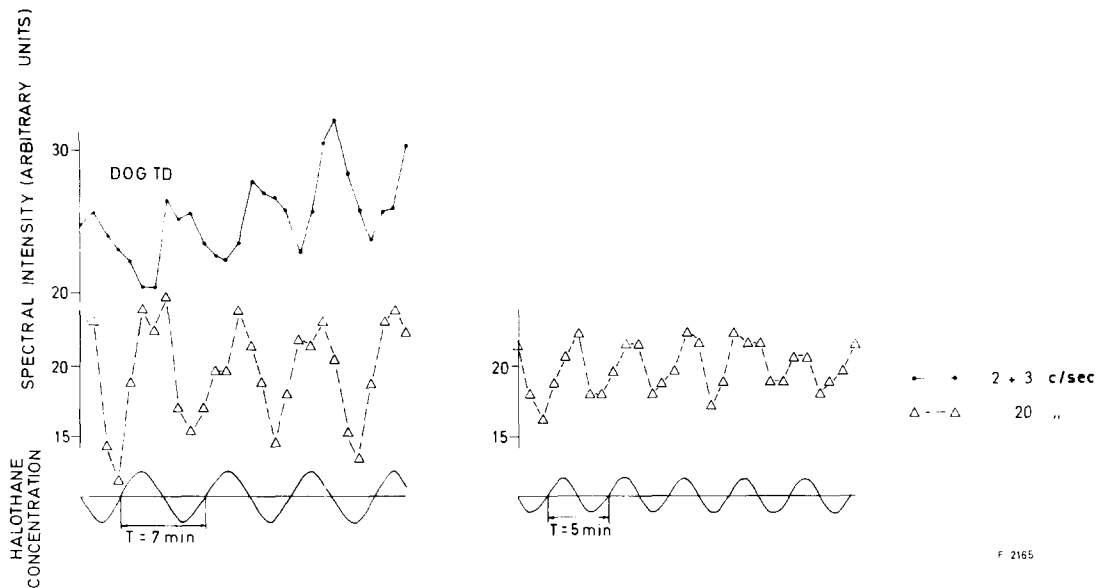
Fig. 4. Variations of intensity of EEG spectral components (arbitrary units) to sinusoidally modulated Halothane concentration: mean value: 1.75%, peak-to-peak values: 0.5 and 3% (inspired air); period T = 7 min (on the left) and T = 5 min (on the right). Each spectral intensity point is the amplitude of one or more filters integrated over preceding 60 sec. Results are for one dog. On the left the variations in spectral intensity of 2–3 c/sec and 20 c/sec with T = 7 min are shown. On the right only EEG component 20 c/sec is depicted for T = 5 min. Note that the EEG spectral intensities vary with the same period as that of the Halothane modulation and that the components 2–3 c/sec and 20 c/sec are out of phase. The decrease in period from T = 7 min to T = 5 min results in a decrease in amplitude of spectral intensity variations.

this level was around 1% the 4–6 c/sec frequency components tended to respond more promptly whereas, when the concentration was higher, the 2–4 c/sec components responded most rapidly. In any case, the rise time of the step responses varied very little. In the positive direction (increase in Halothane concentration) it was found to fall in the range 120–400 sec, calculated as the time necessary for the spectral amplitude to reach 90% of its final value. The decay time (time necessary for the spectral amplitude to decrease to 10% of its initial value) was in the same range of 100–400 sec.

b. *Sinusoidal modulation*

The EEG responses at several periods, T, of sinusoidal modulation were systematically investigated: T = 2, 5, 7 and 11 min. The most sensitive EEG spectral components were found in the frequency ranges 2–6 c/sec and 14–20 c/sec. These components followed the sinusoidal modulation with a periodic oscillation of their amplitude with the same period as the input, although with a phase shift and some distortion

(Fig. 4). This figure shows that the reactivity of components at 14–20 c/sec differs from that of components at 2–6 c/sec. Therefore the phase shifts between them. Indeed the spectral intensity of 14–20 c/sec components increased in the range from 1% up to about 1.75% but decreased gradually at higher concentrations, in contrast with the 2–6 c/sec components. This can be seen in Fig. 2, where the intensity of the components 14–16 c/sec is maximal at 1.5% and decreases at higher concentrations. A phenomenon of adaptation was detected in only one dog, *i.e.*, the response to the first period of Halothane modulation was much larger than the responses to the following periods. In all the others, the responses maintained the same aspect in the course of time although they showed some variability (Fig. 4). To decrease the influence of these fluctuations, an average response was constructed by summing successive periods. The average spectral responses (note that the spectral intensity is the average amplitude of a filter) showed some distortion, especially at low modulation frequencies.

TABLE I

Average spectral intensity responses to sinusoidally modulated Halothane concentration in inspired air.

| Modulation period T | Spectral parameter c/sec | Dog | Absolute spectral intensity* (arbitrary units) | |
|---|---|---|---|---|
| | | | maximal value mean ± s.d. | minimal value mean ± s.d. |
| 11 min | 4 | Br | 36.5 ± 1.4 | 23.6 ± 1 |
| | 4 | N | 34 ± 8.5 | 21.5 ± 0.3 |
| | 2 | H | 25.5 ± 0.5 | 19 ± 1.4 |
| 7 min | 4 | Br | 31.5 ± 4 | 25 ± 1 |
| | 4 | N | 30.5 ± 7 | 20 ± 1 |
| | 2 | H | 31.5 ± 1.1 | 25.5 ± 0.9 |
| 5 min | 4 | Br | 31 ± 1 | 27 ± 1 |
| | 4 | N | 25 ± 0.3 | 22.7 ± 1.8 |
| | 2 | H | 30.3 ± 0.5 | 28 ± 1 |

* The difference between maximal and minimal values is the peak-to-peak amplitude of the variation in spectral intensity (of the chosen frequency component) which follows the sinusoidal modulation of Halothane concentration.

However, the fundamental component was the dominant, so that it did not appear necessary to process these average responses further in order to measure the peak-to-peak amplitude as indicated in Table I; the standard deviations of the mean maxima and minima of the spectral intensity (absolute values) in two cases, dog N: T = 11 and T = 7 min, are particularly large. This results from the fact that, in this dog, the response to the first period of modulation was much larger than the subsequent responses which showed the phenomenon that we called adaptation. In these two cases, and also in dog Br: T = 7 min, it can be observed that the maximal and the minimal means have distinct variances, which suggests that non-linear processes are involved. Notwithstanding all these limitations, it is still possible to conclude from this Table that at increasing frequencies of modulation the mean peak-to-peak amplitude of the spectral response decreases. Taking the amplitude (difference between maximum and minimum) at T = 11 min as 100%, it decreases to 30, 18 and 35% at T = 5 min for the three dogs of the Table. At T = 2 min no EEG changes could be detected. The break point of the high frequency cut-off could not be estimated because the response at T = 11 min was already attenuated in relation to the very low frequency response. Two measurements at T = 19 min indeed showed larger responses but the conditions of stability were difficult to main-tain for the long epochs necessary to obtain a sufficient number of modulation periods to be averaged. This point will be further treated in the Discussion.
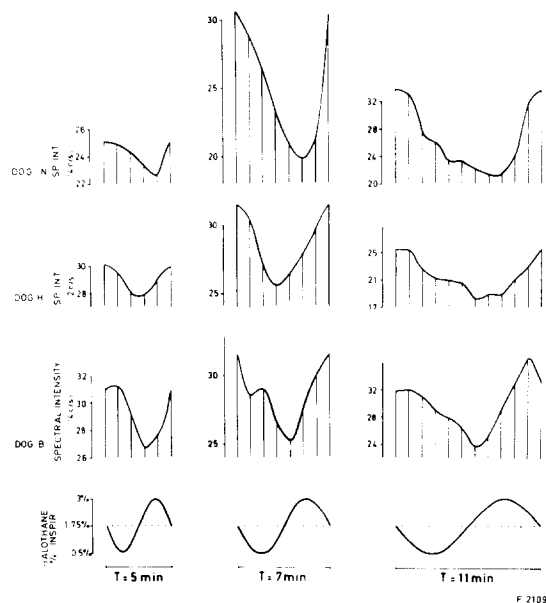


Fig. 5. Average EEG spectral responses to sinusoidally modulated Halothane concentration. One period is shown for the modulations at T = 5, T = 7 and T = 11 min for three dogs. The gain has been halved in the right column. Note the distortion of the responses, particularly at T = 11 min, the decrease in amplitude at decreasing frequencies of modulation and the phase shift between input and output (EEG spectrum). These results are summarized in Table I.

c. *Steady-state levels*

It was not possible to obtain for every dog a relationship between the EEG spectral intensity and the Halothane dose maintained at a steady level (at least for 15 min), *i.e.*, a dose–response relation. The long term stability of the EEG at constant Halothane concentration was, for some dogs, insufficient to obtain reliable results, although the dynamic responses were readily reproducible. However, in one dog it was possible to construct the dose–response relation which is reproduced in Fig. 6. In this respect, the most reliable EEG parameters were the low frequency components (2–3 c/sec). The relation found was approximately linear in the range from 1 to 2.5 $\%$ Halothane concentration in expired air. It should be noted that in this dog the $P_aCO_2$ was kept during the experiment between 30.3 and 31.2 mm Hg.

d. *Relation between EEG changes and other variables*

Increases in intensity of EEG spectral components (2–6 c/sec) following increases in Halothane concentration were associated with decrease in blood pressure, transient increase in heart rate, decrease in stroke volume and in cardiac output. Most of these parameters showed the same response times as the EEG spectrum. A detailed description will be published elsewhere.

In the conditions of the experiments $P_aCO_2$, $PO_2$ and pH did not vary significantly. In Fig. 7 it can be seen that the expired percentage of $CO_2$ did not change significantly during a step increase in Halothane concentration. In a few experiments $CO_2$ was deliberately decreased by means of hyperventilation. The result of respiratory alkalosis, $P_aCO_2 = 19$ mm Hg, was an increase in spectral intensities in the range from 2 to 8 c/sec.

Respiratory acidosis, produced by adding 5.8 $\%$ $CO_2$ to the anaesthetic mixture for about 13 min ($P_aCO_2 = 44$ mm Hg) while keeping Halothane constant, resulted in a decrease in spectral intensities, both of the low and the high frequency components, but particularly of the latter. (It should be noted that in the dog a $P_aCO_2$ of 28–32 mm Hg is normal, *i.e.*, required to maintain a blood pH of 7.38–7.42.)
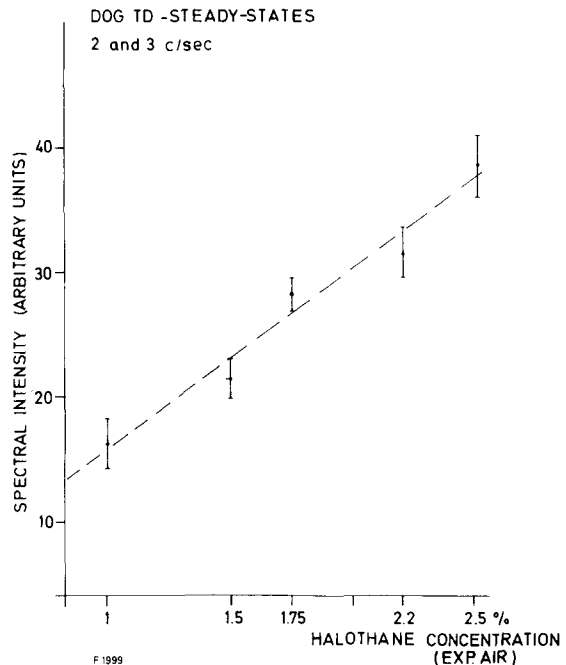


Fig. 6. Spectral intensity of EEG frequency components (band 2–3 c/sec) at Halothane concentrations ($\%$ expired air) maintained constant over a period of more than 15 min. Mean values of 11 measurements taken at 1 min intervals and sample standard deviations are shown. The line was drawn by hand. Note that dose–response relationship is approximately linear.
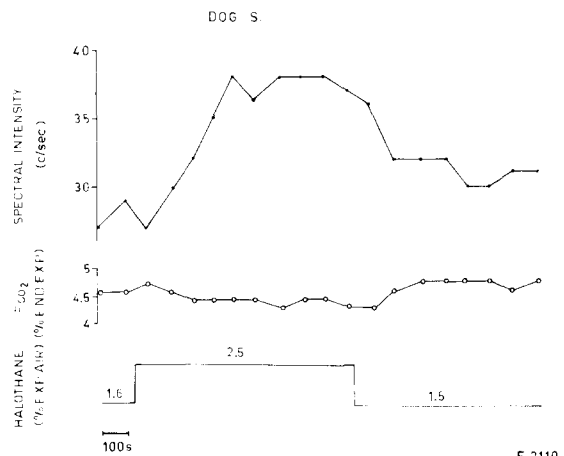


Fig. 7. EEG spectral responses to a step increase in Halothane concentration followed by a step decrease. Below is shown the $PCO_2$ (end expiratory) measured simultaneously with a Capnograph. Note the negligible change in $PCO_2$ with the increase in Halothane concentration and the relatively small increase of $PCO_2$ which accompanies the decrease in Halothane concentration.

DISCUSSION

In this investigation the objectives were (a) to determine which, if any, spectral components of the EEG could give relevant information about the depth of Halothane anaesthesia and, in case those EEG parameters could be defined, (b) to determine their dynamic response to changes in Halothane concentration. Spectral components of the EEG were indeed found to give relevant information about Halothane anaesthesia, the most sensitive being in the frequency ranges 2–6 c/sec and 14–20 c/sec.

The dynamics of the system were investigated by step and sinusoidal functions. The step functions enabled us to determine the transient response of the system, to note that it behaves approximately as an integrator and to observe that it responds similarly to increases (positive steps) and to decreases (negative steps) in Halothane concentration, at least in the range 1–3%. There was considerable variation among dogs with regard to the system's transient response; the rise times were, for four dogs, in the range 120–400 sec and the decay times were 100–400 sec. Sinusoidal modulation was used to investigate the system's dynamics under steady-state conditions. This type of modulation enabled us to test the linearity of the system and the type of integrator. One important non-linearity was found: there was a two-way "saturation", i.e., as the Halothane concentration in inspired air decreased to about 0.5%, the intensity of the most sensitive spectral components (2–6 c/sec) did not decrease monotonically, and as the Halothane concentration increased above $3°_o$, it did not continue to increase. On the contrary, it started decreasing progressively. In the case of the components 14–20 c/sec the decrease occurred at even lower concentrations (below 2%). This implies that to monitor the depth of Halothane anaesthesia at low and at high concentrations one has to make use of more information about the EEG spectrum than simple measurements of spectral intensities in a few bands.

The most important aspect that can be deduced from the sinusoidal responses is that they show that the system behaves as a low pass filter, whose attenuation and phase characteristics

differ somewhat from those of a simple integrator (one-pole system). These characteristics varied appreciably from dog to dog so that it was not possible to deduce a general exact model of the system.

Another interesting aspect was that it was possible to construct a dose–response linear relationship for Halothane–EEG spectrum in one dog between 1 and 2.5%. It may be that this was not possible in other dogs because the conditions of the experiment were less stable.

The question remains whether the EEG changes found during Halothane anaesthesia are the direct consequence of the uptake of Halothane by the brain or are an indirect effect of changes in other parameters such as $CO_2$ (Backman et al. 1964) or blood flow. The fact that, in our experiment, $PCO_2$ was maintained within strict limits (see Fig. 7) rules out the first case. It should be emphasized, however, that changes in $PCO_2$ may cause also changes in the EEG spectrum, as mentioned in Results. As far as blood flow is concerned, it is worth mentioning that Theye and Michenfelder (1968) showed that Halothane reduced the rate of consumption of $O_2$ by the brain while increasing cerebral blood flow. Some studies point in the same direction (Wollman et al. 1964), but there are others which report a decrease in blood flow during Halothane anaesthesia (Christensen et al. 1965). Further investigation is necessary.

One practical aspect must still be discussed. In this study we have considered as the relevant EEG parameter, the spectral intensity (in terms of amplitude and not of power, although this is not a crucial point) of several frequency components.

We observed that the response of different components did not always have the same time course (see Fig. 4). This might suggest the use of some other EEG parameter such as the frequency of the peak of the power spectrum (Findeiss et al. 1969) or the average frequency, as in a study of the EEG frequency response to thiopental (Schwartz et al. 1971), or a coefficient of frequency shift, as we have used in another study (Kamp et al. 1971). Indeed we also found shifts in the dominant frequencies of the EEG spectrum, as reported in Results. However, the variation in spectral intensity was preferred because, on the

one hand, it appeared to give most of the relevant information and, on the other, it provided a simple parameter both to measure and to interpret.

In conclusion, the intensity of EEG spectral components provides a useful sign to use in a monitoring system of Halothane anaesthesia, taking into account the rise and decay times of the system. To perform this monitoring in practice, a simple system consisting of selected analogue band-pass filters and integrators can be a useful device, taking into consideration cost and effectiveness. However, in a general monitoring system for anaesthesia other parameters (cardiovascular, ventilation and blood gases) are indispensable.

We think that the present study may serve as an introduction to the development of practical systems in which the EEG will have a place in anaesthesia monitoring.

SUMMARY

1. The "Halothane-brain compartment" system was investigated in dogs. The input was the inspired concentration of Halothane. The output was the intensity of EEG spectral components. The EEG was analysed by a hybrid system (analogue filters and digital integration in a small computer). For the anaesthesia only a mixture of Halothane and oxygen was used. Temperature, $CO_2$ and pH were kept constant.

2. Input–output relations were determined by recording responses to step and sinusoidal changes of concentration. The most sensitive output parameters were the intensities of the 2–6 c/sec and 14–20 c/sec components.

3. The rise and decay times of the responses to positive and negative steps were in the range 120–400 sec and 100–400 sec (5 dogs), respectively.

4. The sinusoidal average responses showed some distortion, particularly at low frequencies of modulation (T = 11 min), indicating the existence of non-linearities. Evidence for the phenomena of adaptation and saturation was also found. Attenuation of response amplitude and increase in phase shift were found as frequency of modulation was increased, as in a low pass filter. With the data available it was not possible to determine the order of the linear approximation to the system with sufficient accuracy.

5. A dose–response linear relation within the range of Halothane in inspired air between 1.0 and 2.5 % was obtained for one dog.

6. It is proposed that the quantitative data obtained in this study provide a basis for constructing a reliable monitoring system of Halothane anaesthesia.

RESUME

ANALYSE SPECTRALE DE L'EEG AU COURS DE L'ANESTHESIE PAR HALOTHANE: RELATIONS ENTREE–SORTIE

1. Le système "Halothane-compartiment cérébral" est étudié chez le chien. L'entrée est la concentration d'Halothane inspirée. La sortie est l'intensité des composantes spectrales de l'EEG. L'EEG est analysé par un système hybride (filtres analogiques et intégration digitale dans un petit ordinateur). Pour l'anesthésie, un simple mélange d'Halothane et d'oxygène a été utilisé. La température, le $CO_2$ et le pH ont été maintenus constants.

2. Les relations entrée–sortie sont déterminées par les réponses enregistrées à des modifications abruptes et sinusoïdales de la concentration d'Halothane. Les paramètres de sortie les plus sensibles sont les intensités des composantes de 2–6 c/sec et 14–20 c/sec.

3. Les temps d'accroissement et de décroissance des réponses à des variations abruptes positives et négatives se situent entre 120 à 400 sec et entre 100 à 400 sec respectivement (5 chiens).

4. Les réponses moyennes sinusoïdales montrent une certaine distorsion, particulièrement à des fréquences basses de modulation (T = 11 min), indiquant l'existence de non-linéarités. On observe également des signes en faveur de l'existence de phénomènes d'adaptation et de saturation. L'atténuation de l'amplitude de la réponse et l'augmentation de variations de phase s'observent lorsque la fréquence de modulation est augmentée, de même que dans les filtres passe-bande bas. Avec les données disponibles, il n'est pas possible de déterminer l'ordre d'approximation linéaire du système avec une précision suffisante.

5. Une relation linéaire dose–réponse a été obtenue chez un chien lorsque la quantité d'Halothane dans l'air inspiré se situe entre 1,0 et 2,5%.

6. Les auteurs concluent que les données quantitatives obtenues dans cette étude, fournissent une base devant permettre la construction d'un système de contrôle valable de l'anesthésie par Halothane.

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