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Alterations in Brain Electrical Activity May Indicate the Onset of Malignant Hyperthermia in Swine

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The time course of changes in brain electrical activity during halothane anesthesia was examined in 12 malignant hyperthermia-susceptible (MHS) and 14 normal (nMHS) swine. Power densities in selected frequency bands were calculated from the electroencephalogram (EEG). EEG and systemic variables were determined over a period of 60 min after starting halothane (1% inspired). Malignant hyperthermia (MH) was triggered in all susceptible pigs. Initial changes in the EEG during development of MH consisted of a decrease in total power and a shift to lower frequencies (delta–theta activity) in all animals. These EEG alterations were noted when there was an increase in heart rate, but other systemic variables were still normal. EEG changes in all MHS animals started at an arterial oxygen tension (Pa_{O_2}) greater than 90 mmHg and an arterial carbon dioxide tension (Pa_{CO_2}) less than 50 mmHg. In 5 MHS animals EEG became isoelectric at a Pa_{O_2} of 61–82 mmHg and a Pa_{CO_2} of 53–68 mmHg. Mean arterial blood pressure at this time was 54–66 mmHg. To determine the effects of hypoxia on the EEG in 7 nMHS animals, oxygen was decreased over a period of 45–60 min to 7% inspired. In 7 other nMHS animals, hypercarbia was produced by admixture of carbon dioxide to the fresh gas supply to achieve incremental increases of Pa_{CO_2} to 110–120 mmHg. Significant EEG changes during hypoxia comparable to those seen at the onset of MH were noted at a Pa_{O_2} below 40 mmHg and during hypercarbia at a Pa_{CO_2} greater than 68 mmHg. Our results do not support the hypothesis that early EEG changes during MH occur as a result of systemic hypotension, hypoxemia, or hypercarbia. (Key words: Anesthetics, volatile: halothane. Animals: Pietrain pigs, German Landrace pigs. Brain: electroencephalography. Hyperthermia: malignant pyrexia. Hypnotics, barbiturate: methohexital. Hypoxia: induced hypoxia. Hypercarbia: induced hypercarbia.)

NEUROLOGIC SEQUELAE of patients surviving a fulminant malignant hyperthermia syndrome (MH) may include areflexia, acute cerebral edema, seizures and coma.[1–3] Electroencephalography (EEG) may be of value in detecting altered function of the central nervous system (CNS) associated with these complications. However, EEG changes have not been related temporally to the development of hemodynamic, respiratory, and metabolic changes during a fulminant MH crisis. Artru and Gronert[4] found no increase in brain lactate production or cerebral oxygen consumption during halothane- and succinylcholine-induced MH in susceptible swine. Although they concluded that the brain was not primarily involved in the development of MH, the time of onset of EEG changes in relation to other systemic changes in MH is unclear. The current study was designed to assess the time course of changes in brain electrical activity during a halothane-induced MH crisis in swine in relation to systemic hemodynamic, respiratory, and metabolic parameters. The effects of hypoxia and hypercapnia on the EEG of non-MH-susceptible (nMHS) pigs also were studied to determine whether these challenges are capable of inducing the EEG changes seen in MH crisis.

Materials and Methods

12 MH-susceptible (MHS) swine from a colony of Pietrain pigs (22–40 kg, age 3–6 months) whose lines have been maintained for the past 10 yr and 14 nMHS pigs (German Landrace, 32–48 kg, age 4–6 months) were studied. The procedures used in the experiment were approved by the veterinary ethical committee and were performed in accordance with the legal regulations for laboratory animals.

TEST FOR MH-SUSCEPTIBILITY

In order to evaluate MH susceptibility,¶ all pigs at the age of 4–6 weeks had been challenged by exposure to 7% halothane in oxygen (6 $l \cdot min^{-1}$). All gases were administered from an anesthetic machine with a semiclosed circle delivery system *via* a face mask for a period of up to 4 min. The Pietrain pigs responded within 60–105 s with rigidity of the pelvic limbs, which abated after the immediate withdrawal of halothane. These pigs were classified as MHS. None of the Landrace pigs demonstrated unusual symptoms during halothane exposure and were classified as nMHS.

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¶ Eikelenboom G, Minkema D: Prediction of pale, soft, exudative muscle with a non-lethal test for halothane induced porcine malignant hyperthermia syndrome. Netherlands Journal of Veterinary Science 99:421–426, 1974.

Experimental Protocol

Each animal was fasted overnight with free access to water. Ten to 15 min after intraperitoneal injection of azaperon (Stresnil®) 30–50 mg and metomidate hydrochloride (Hypnodil®) 10 mg · kg^{-1} methohexital 100–150 mg iv was given. After laryngeal administration of lidocaine 4% and manual hyperventilation with 100% oxygen (3–5 min) the trachea was intubated. Mechanical ventilation (Engstroem 300®) was set to maintain end-expiratory carbon dioxide tensions (PET_{CO_2}; Capnograph®) of 33–38 mmHg. Throughout the study anesthesia was maintained by methohexital 25–40 mg · h^{-1} and 50% nitrous oxide in oxygen. Before control recordings, the methohexital dose was titrated to a median EEG frequency of 4–5 Hz. During surgical preparation, incremental doses of fentanyl were given to a total dose of 25 μg · kg^{-1}. Mean arterial blood pressure (MAP) was monitored *via* a femoral artery catheter. A triple lumen catheter (5F, Corodyn®) was inserted into the pulmonary artery for measurement of cardiac index (CI)[5] by the thermodilution technique. Body temperature was monitored *via* a pulmonary artery thermistor. During the control period, body temperature was maintained at 35.5–37° C in nMHS and at 36.5–38° C in MHS pigs by means of a warming pad.

During surgery, Ringer's solution was given iv at a rate of 50–150 ml · h^{-1}. Glucose 5% was substituted if plasma concentrations were less than 120 mg · dl^{-1} and titrated to achieve a plasma concentration between 150 and 200 mg · dl^{-1}. All pigs were paralyzed with vecuronium (2–3 mg · h^{-1}). After surgical preparation stable hemodynamic conditions were established over 60–90 min. After control data were obtained, halothane (1% inspired) was administered to all animals. The infusion rate of Ringer's solution was increased to 200–400 ml · h^{-1}.

In the nMHS control group, 60 min after starting halothane the effects of hypoxia and hypercapnia were studied. The animals were randomly assigned to one of two groups. In seven animals (nMHS group 1), hypoxia was achieved over a period of 45–60 min by administration of nitrous oxide in increasing concentration with a lower limit of 6–7% inspired oxygen. In seven other animals (nMHS group 2), hypercarbia was studied over a period of 45–60 min by delivering carbon dioxide in incremental concentration to the inspired gases increasing the Pa_{CO_2} in 10–15-mmHg increments to a maximum of 110–130 mmHg.

EEG

Platinum needle electrodes for EEG recordings were placed above secondary association fields at a position corresponding to the vertex in humans (Cz) with linked earlobes (A1–A2) as a reference and at parietal sites above the somatosensory projection areas (F1 and F2, corresponding to C3 and C4 in humans) *versus* a frontal reference (Fz). The electrooculogram (EOG) was recorded from supra- *versus* infraorbital electrodes. The interelectrode impedances were less than 5 kohm (12 Hz). Bandpass for EEG- and EOG-recordings was set at 0.5–45 Hz. The EEG power spectra were analyzed after Fourier transformation (FFT, epoch length 5.2 s, digitization 100/s). Integrated EEG power was calculated for selected frequency bands as follows: delta 0.5–3.9 Hz, theta 4.0–7.9 Hz, alpha 8.0–12.9 Hz, beta 1 13–17.9 Hz, and beta 2 18.0–45.0 Hz).

In the MHS group all animals were studied until death. In all groups analog data (EEG, ECG, AP, PET_{CO_2}, and EOG) were recorded continuously and stored on magnetic tape (Store 7DS®). Triplicate CI measurements and blood gas analyses of mixed venous and arterial blood were repeated every 5 min. Blood samples were obtained for measurement of plasma Na^+, K^+, and Cl^- every 5 min and for glucose every 30 min.

All results are expressed as mean ± SD. Comparisons were made by analysis of variance for repeated measurements, followed by *t* tests with Bonferroni corrections. Statistical significance was assumed at $P < 0.05$.

Results

Halothane Administration (nMHS and MHS Groups)

Systemic Parameters

Table 1 and figure 1 give heart rate (HR), MAP, CI, Pv_{O_2}, and Pv_{CO_2} arterial *p*H and potassium plasma concentration data. With the exception of body temperature (nMHS 36.2 ± 0.4, MHS 37.2 ± 0.6° C) control data were not different between groups. In both groups, administration of halothane decreased MAP by 10–20% and increased HR by 15–25%. All systemic parameters did not change significantly for the time period 15–27 min following exposure to halothane. However, 31 min (range: 27–36 min) after the start of halothane administration, the MHS animals showed changes in hemodynamic and ventilatory parameters. Within the next 15 to 30 min an abrupt increase in HR and transient increases in MAP and CI followed by decreases below baseline recordings were noted. Pa_{CO_2} increased to 89 ± 12 mmHg 45 min after the start of halothane administration. At about the same time arterial *p*H decreased to 7.11 ± 0.14, plasma potassium increased to 8.8 ± 1.4 mEq · l^{-1}, and Pa_{O_2} was 74 ± 18 mmHg. The first significant increase in body temperature was noted 5 to 10 min after changes in hemodynamic variables had occurred. All MHS animals died within 53–65 min after the start of halothane exposure. At this time body temperature was 40.9 ± 1.7° C.

TABLE 1. EEG Total Power, Hemodynamic Parameters, and Plasma K^+ Before and After Addition of Halothane (1% Inspired)

	EEG ($\mu V^2/Hz$)		HR (beats per min)		MAP (mmHg)		CI ($l \cdot kg^{-1} \cdot min^{-1}$)		K_a^+ ($mEq \cdot l^{-1}$)	
t (min)	nMHS	MHSS	nMHS	MHS	nMHS	MHS	nMHS	MHS	nMHS	MHS
Control	136 ± 25	145 ± 27	99 ± 20	93 ± 18	86 ± 19	89 ± 20	0.105 ± 0.031	0.099 ± 0.021	4.9 ± 0.7	5.0 ± 0.6
20	161 ± 31	159 ± 33	108 ± 19	104 ± 21	74 ± 22*	76 ± 18*	0.088 ± 0.021*	0.082 ± 0.024*	4.9 ± 0.6	4.9 ± 0.6
30	158 ± 28	136 ± 31†	103 ± 29	117 ± 29*·†	73 ± 17*	79 ± 21	0.085 ± 0.021*	0.088 ± 0.025	4.8 ± 0.6	5.1 ± 0.7
35	149 ± 30	99 ± 25*·†	102 ± 28	123 ± 33*·†	71 ± 15*	84 ± 25†	0.089 ± 0.020*	0.097 ± 0.029	4.9 ± 0.6	5.2 ± 0.7
40	158 ± 31	74 ± 26*·†	106 ± 28	141 ± 39*·†	66 ± 13*	121 ± 25*·†	0.086 ± 0.023*	0.137 ± 0.031*·†	4.9 ± 0.8	5.8 ± 0.9*·†
45	163 ± 28	52 ± 22*·†	101 ± 30	188 ± 49*·†	65 ± 12*	139 ± 29*·†	0.089 ± 0.021*	0.149 ± 0.033*·†	4.9 ± 0.7	8.8 ± 1.4*·†

MHS = MH-susceptible swine (n = 12); nMHS = nonsusceptible swine (n = 15); HR = heart rate; MAP = mean arterial blood pressure; CI = cardiac index; K_a^+ = arterial plasma potassium.
$P < 0.05$: **versus* control data; †*versus* nMHS animals.

EEG

In both groups the EEG during control recordings (anesthesia with methohexital and nitrous oxide) was dominated by delta–theta activity (20–45% of total power) superimposed by higher-frequency activity (fig. 2). The EEG was not contaminated by EOG artifacts, which may stimulate low-frequency activity in the delta–theta range. In both groups, exposure to halothane resulted in superimposed 14–26 Hz activity and a moderate increase ($P < 0.07$) in total power (fig. 3). In contrast, in the MHS animals total power started to decrease after 26–30 min of halothane administration. At the same time, halothane-induced beta-activity disappeared and a significant shift to lower frequencies occurred. Polymorphic delta activity became dominant in the course of the now clinically obvious MH crisis (40–50 min after halothane). In five animals, brain electrical activity disappeared despite hemodynamic (MAP 54–66 mmHg) and respiratory conditions (Pa_{O_2} 61–82 mmHg, Pa_{CO_2} 53–68 mmHg)

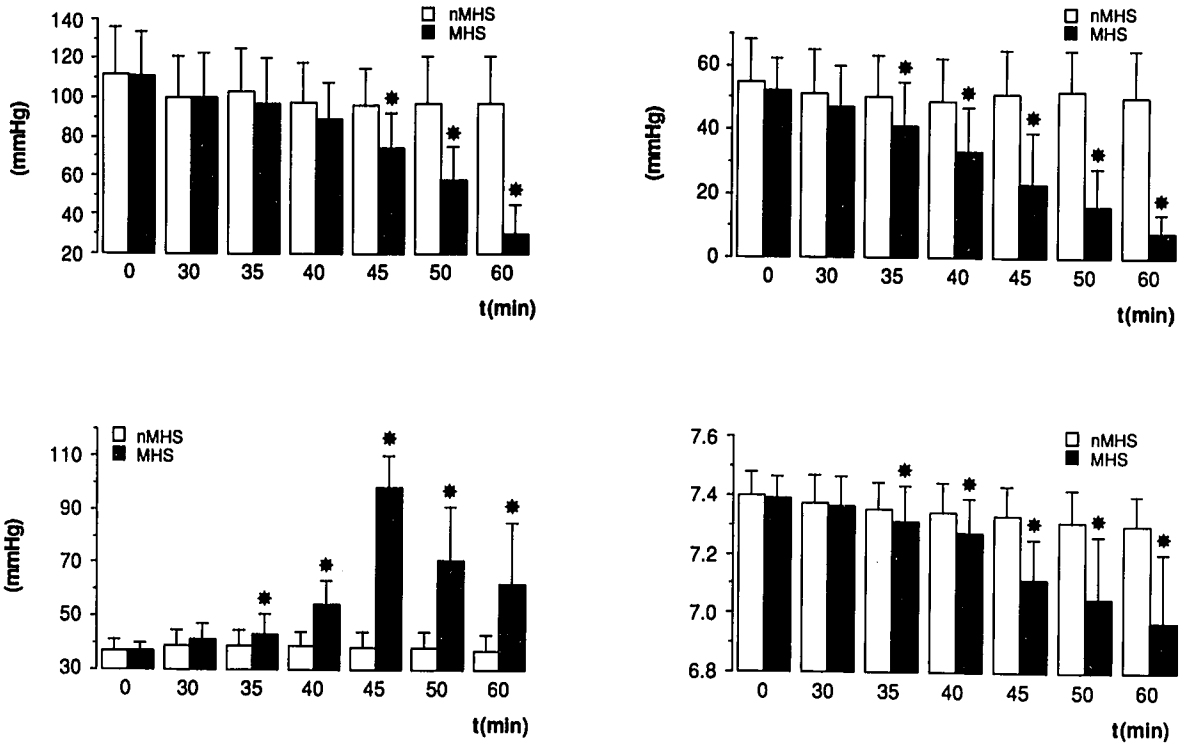

FIG. 1. Arterial (Pa_{O_2}), mixed venous (Pv_{O_2}), arterial carbon dioxide (Pa_{CO_2}) tensions, and arterial *p*H in MHS (n = 12) and nMHS (n = 14) swine after exposure to halothane (1% inspired). *$P < 0.05$ *versus* control data.

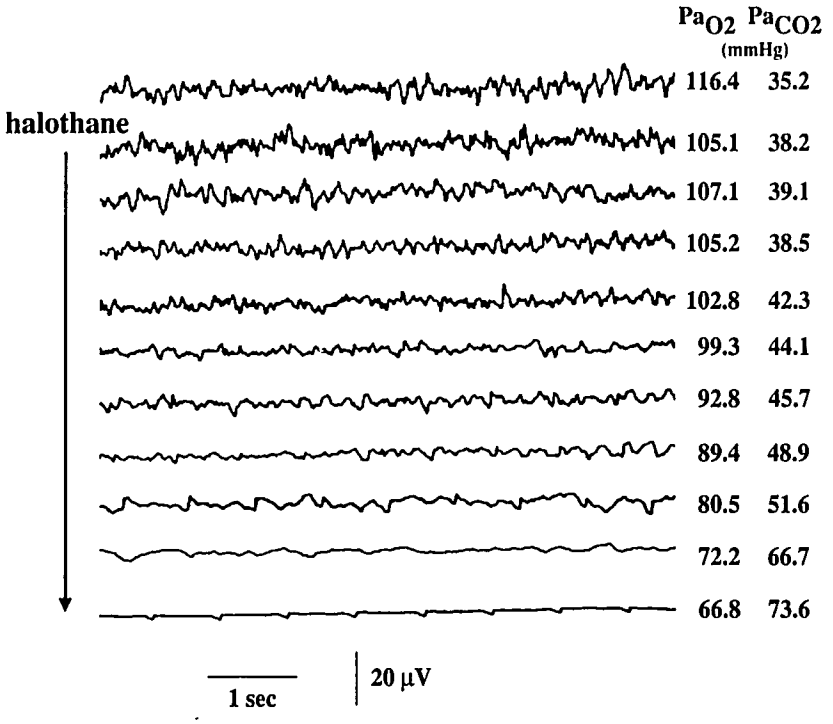

FIG. 2. Original recordings of an MHS animal (MHS 648111) before (first tracing) and during exposure to halothane (1% inspired) in addition to 50% nitrous oxide and methohexital iv (25–40 mg · kg^{-1}). Corresponding Pa_{O_2} and Pa_{CO_2} data are given on the right. Clearly visible is the onset of EEG deterioration at almost unchanged Pa_{O_2} and Pa_{CO_2} (fifth and sixth tracings from the top).

compatible with life. In two other animals, intermittent spike-wave activity occurred. In these animals body temperature and Pv_{O_2} were not different from the findings in the other MHS animals.

HYPOXIA (nMHS GROUP 1)

In order to study the effects of hypoxia on EEG and systemic parameters, seven nMHS pigs were tested. Baseline hemodynamic, ventilatory, and EEG parameters were recorded after 60 min of exposure to halothane.

Systemic Parameters

The first significant change in hemodynamic parameters during progressively increasing hypoxia occurred at Pa_{O_2} values less than 65 mmHg (table 2). Below a Pa_{O_2} of 35–40 mmHg, MAP and CI progressively decreased, and finally at MAP less than 55 mmHg and CI less than 0.065 l · kg^{-1} · min^{-1}, four animals died.

EEG

The earliest EEG changes during hypoxia occurred at a Pa_{O_2} of 55 ± 12 mmHg. These included a decrease in beta activity followed by a shift to lower frequencies. However, a significant shift to predominantly delta–theta activity eventually leading to a complete loss of EEG activity occurred only at an inspired oxygen concentration less than 7% at Pa_{O_2} values of 25–30 mmHg (table 2). Pa_{CO_2} at this time was 32–41 mmHg.

HYPERCARBIA (nMHS GROUP 2)

The effects of hypercarbia on systemic and EEG parameters were studied in another group of seven animals.

Systemic Parameters

Hemodynamic responses resulting in increases in HR, MAP, and CI were obvious at a Pa_{CO_2} of ± 5 (table 2). Three animals died during the most severe hypercarbia.

EEG

Compared to hemodynamic responses, the first EEG changes occurred at Pa_{CO_2} levels above 68 ± 5 mmHg. An overall shift to predominantly delta activity and a decrease in total power was noted at Pa_{CO_2} values higher than 70–80 mmHg (mean 76 ± 5 mmHg). At a Pa_{CO_2} greater than 100 mmHg, delta activity supervened and electrical silence occurred in three animals during this extreme hypercarbic condition.

Discussion

These results show that significant EEG depression may precede the onset of cardiovascular and metabolic changes in halothane-induced MH. In addition, the EEG effects seen during the onset of MH, do not show a close correlation with the brain electrical effects of hypoxia or hypercarbia alone in nMHS pigs. These findings suggest that during the onset of MH other systemic factors not

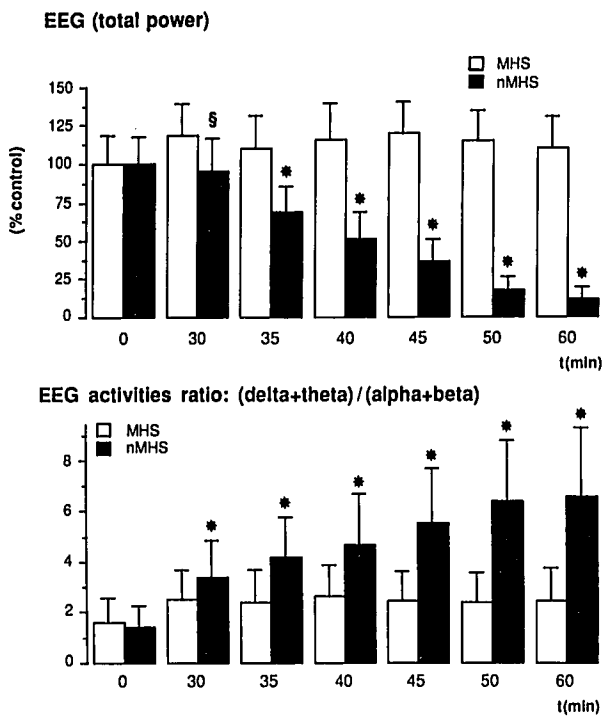

FIG. 3. (*Top*) Total power spectrum density (percent of control) during control recordings (t = 0) and after the addition of halothane (1% inspired) in addition to 50% nitrous oxide and methohexital iv (25–40 mg · kg^{-1}) in non-MH-susceptible (nMHS; n = 14) and MH-susceptible swine (MHS; n = 12). (*Bottom*) Ratio of EEG activities in delta (0.5–3.9 Hz) plus theta (4.0–7.9 Hz) to alpha (8.0–12.9 Hz) plus beta (13.0–45 Hz) bands. MH-triggering leads to significant decreases in total spectral density power and a shift to lower frequencies as reflected by an increase in EEG activities ratio. Bandpass: 0.5–45 Hz; recording site: vertex *versus* linked earlobes; significance: $P < 0.05$; *MHS *versus* nMHS; §first significant changes during MH in the same group *versus* previous time interval.

measured in this study are responsible for altered EEG activity or that the CNS is primarily involved in the development of MH.

Comparison of our findings with those of other investigators is difficult because previous MH studies have not focused on the time course of EEG changes in relation to changes in other systemic variables. In a study on succinylcholine-halothane-induced MH, Artru and Gronert[4] concluded that the brain is not primarily involved in MH. Brain metabolism and lactate production were unchanged during the early development of MH. However, they observed EEG depression when Pa_{O_2}, Pa_{CO_2}, cerebral lactate production, cerebral oxygen consumption, arterial *p*H, plasma catecholamines, and body temperature were not different from control. Although we agree that brain metabolic changes may not be a primary cause of MH, our results clearly do not agree with their conclusion that initial EEG changes are produced because of MH-induced hypoxia and hypercapnia. The time intervals evaluated may explain the different conclusions: we measured EEG continuously during the development of MH, and Artru and Gronert[4] evaluated EEG after development of MH. In addition, the rapid onset of MH seen in their studies after succinylcholine-halothane-induced MH makes it difficult to interpret the time course of initiating factors. With a longer period of MH development and careful analysis of the sequence of EEG *versus* hypoxia and hypercapnia, our data suggest that EEG leads, rather than lags behind, changes in hemodynamic, respiratory–ventilatory parameters, plasma potassium levels, and body temperature. On the other hand, during advanced-stage experimental MH, improved EEG activity not related to changes in blood gases or hemodynamics has been demonstrated after MH treatment with dantrolene.[6]

The role of the CNS in the development of MH is controversial. Kerr *et al.*[7] found that MH could not be triggered in MHS animals with high epidural blocks. They concluded that while skeletal muscle is probably the main site of aberrant metabolism in MH, neural mechanisms may be essential for the disease to occur. This was disputed by later studies showing that MH triggering was possible even in the presence of high epidural or intrathecal blockade.[8],** Studies finding brain tissue damage after MH attribute this damage to hypoxia, hypercarbia, electrolyte imbalances, decreased tissue *p*H, and hyperthermia.[4,9–11] The results of Artru and Gronert[4] show that abnormal brain metabolism does not occur in the early stages of MH. However, other mechanisms involving early efferent neuronal activity or local neuronal changes cannot be excluded by the global measurements of their studies.[4] Additionally, interactive effects of small changes in a variety of metabolic, respiratory, and hemodynamic parameters may result in altered brain electrical activity. Higher body temperature in MHS animals seen at control does not reflect triggering of MH, since there was no change in evaluated parameters or clinical evidence for the onset of an MH syndrome. The difference in body temperature during control may be due to an increased metabolic rate at rest. However, in a previous study,[12] no evidence for increased metabolism in MHS subjects either at rest or during exercise could be found. In the current study, the animals of each group were kept in different places. Therefore, it is more likely that differences in body temperature seen at control reflect differences in maintenance.

During systemic hypoxia in nMHS pigs, significant EEG slowing occurred at Pa_{O_2} levels below 40 mmHg. This agrees with previous studies.[13–15] A similar degree of slowing was seen in MH at a time when Pa_{O_2} was normal.

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TABLE 2. EEG, Blood Gas and Hemodynamic Parameters during Hypoxia and Hypercarbia in Nonsusceptible Swine

	EEG (Total Power) (% control)	Pa_{O_2} (mmHg)	Pv_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	*p*Ha	HR (beats per min)	MAP (mmHg)	CI ($l \cdot kg^{-1} \cdot min^{-1}$)
Control	100 ± 34	110 ± 10	58 ± 7	41 ± 5	7.39 ± 0.09	101 ± 20	68 ± 17	0.105 ± 0.025
Hypoxia (25 min)	88 ± 27	40 ± 13*	22 ± 10*	41 ± 6	7.35 ± 0.09	116 ± 25*	121 ± 35*	0.133 ± 0.042*
Hypoxia (30 min)	49 ± 23*	26 ± 11*	14 ± 11*	39 ± 6	7.29 ± 0.12*	144 ± 31*	79 ± 22*	0.071 ± 0.029*
Control	100 ± 28	109 ± 10	60 ± 16	37 ± 3	7.34 ± 0.10	94 ± 23	76 ± 15	0.106 ± 0.024
Hypercarbia (18 min)	120 ± 37	107 ± 13	72 ± 18*	68 ± 5*	7.25 ± 0.14*	136 ± 19*	100 ± 25*	0.125 ± 0.041*
Hypercarbia (25 min)	62 ± 30*	107 ± 14	74 ± 19*	89 ± 10*	7.19 ± 0.15*	146 ± 24*	110 ± 27*	0.135 ± 0.040*

Control data and first significant EEG changes during hypoxia and hypercarbia in nonsusceptible swine (nMHS; n = 7): Pa_{O_2} = arterial P_{O_2}; Pv_{O_2} = mixed venous P_{O_2}; Pa_{CO_2} = arterial P_{CO_2}; *p*Ha = arterial *p*H; HR = heart rate, MAP = mean arterial blood pressure, CI = cardiac index; EEG total power expressed as changes from control (100%). Significance: $P \leq 0.05$, **versus* control recordings.

Measures of global brain function during MH indicate that cerebral hypoxia and lactic acidosis do not occur.[4] This questions whether hypoxia is a primary factor in EEG depression during the early phases of MH.

Similar reasoning can be assumed for the role of Pa_{CO_2} on the EEG. Our data show that during MH, a slowing in EEG and a decrease in EEG power were apparent with a Pa_{CO_2} of 45–55 mmHg. In nMHS, in contrast, similar EEG alterations were not seen until Pa_{CO_2} rose above 65 mmHg. Other investigators also have shown that marked elevations in Pa_{CO_2} (greater than 65 mmHg) are necessary in order to produce significant EEG alterations consisting of enhanced excitability followed by pronounced depression at still higher Pa_{CO_2}.[16] This depression may be associated with a positive shift in the underlying cortical slow wave (DC) potentials,[16] which can be measured only if an infinite time constant (DC amplifier) is chosen. It is unlikely that changes in cortical DC potential occurred here during the initial stages of MH, when Pa_{CO_2} showed only small increases.[16] From this we conclude that in the initial phase of MH a rise in Pa_{CO_2} cannot be the primary factor for altered EEG activity.

Since there is an inverse relationship between Pa_{CO_2} and *p*H, the effect of decreased tissue *p*H on neuronal function must be considered. In a physiologic range vascular resistance in the brain is locally regulated by extracellular *p*H.[17] However, only substantial decreases in blood *p*H (*p*H < 7.08) are associated with marked EEG alterations.[18] Therefore, it seems unlikely that the moderate decreases in arterial *p*H at the time of MH triggering can be considered a major cause for changes in EEG activity. It may be argued that a *p*H gradient exists between cisternal cerebrospinal fluid (CSF), cortical subarachnoid CSF, and local perivascular CSF, which cannot be assessed by plasma *p*H values. However, this is unlikely since cerebral hypoxia or hypercarbia do not occur in the early stages of MH.[4]

Another cause for EEG alterations may be increased potassium blood concentrations usually found during MH.[19] Increased cerebral perivascular and CSF potassium concentrations may dilate pial arteries[17] and thus give rise to an increase in CBF.[20] Elevated potassium blood concentrations evoke considerable change in the DC potential in cortical areas and eventually may suppress EEG activity.[16] However, potassium crosses the blood–brain barrier very slowly, and significant depression in cortical excitability is detected only at blood potassium concentrations above 8 $mEq \cdot l^{-1}$.[21] This value is far above the findings during the onset of MH when first EEG changes are observed. EEG recordings in uremic, acidotic patients as well as those in animals with experimental induced uremia with potassium blood concentrations of 5–6 $mEq \cdot l^{-1}$ did not reveal EEG abnormalities comparable to those seen with MH.[22,23]

In conclusion, our results do not support the hypothesis that changes in Pa_{O_2}, Pa_{CO_2} or blood pressure are the main cause for the EEG changes observed. However, these EEG changes may be induced by systemic parameters not measured here. The brain also may play a role in triggering MH peripherally. Although our data indicate functional involvement of CNS structures during the development of MH, the mechanisms underlying the early EEG alterations are not known. These may happen in response to an increase in circulating hormones or metabolites that have not been defined. Our data indicate that EEG may be relevant for monitoring procedures in MHS patients.

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