

Brain Surface Oxygen Tension and Cerebral Cortical Blood Flow During Drug-induced Hypotension.

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INTRODUCTION

Cerebral blood flow is maintained constantly in man over a range of mean arterial blood pressure (MAP) of 60 to 130 mmHg by cerebral autoregulation¹⁾. In clinical anesthesia, blood pressure is sometimes reduced below the lower limit of autoregulation, in order to improve surgical operating conditions. In this technique two drugs, sodium nitroprusside (SNP) and trimethaphan (TMP), are commonly used. However, cerebral oxygenation during the hypotension induced by these drugs has not been fully studied. We speculated that there might be differences between the different drugs in oxygenation of the brain and cerebral perfusion, since the mechanisms of action of the drug differ^{2,3)}. Accordingly, these possibilities have been explored by measuring oxygen pressure (P_{bO_2}) at multiple sites on the cortical surface in cats, and by measuring regional cerebral blood flow (rCBF) from the same area during hypotension induced by SNP or TMP, and it was concluded that cerebral oxygenation during SNP hypotension was maintained better than during TMP hypotension.

METHOD

Studies were made in 10 cats weighing 2.0 to 3.2 kg. They were anesthetized in a case, using 3 per cent halothane in oxygen. As soon as consciousness was lost, the concentration of halothane was reduced to 1 per cent and 40 mg of intramuscular succinylcholine was given for orotracheal intubation with a cuffed tube. Ventilation was controlled, thereafter, with a Starling animal ventilator set to produce normocapnia (30 mmHg in the cat), and muscle paralysis was maintained with intramuscular pancuronium, 2 mg initially and 0.5 mg following every 30 min. A rectal thermocouple probe measured temperature, which was maintained at 38°C using an electric heating blanket.

The surgical preparation started with bilateral catheterization of both

femoral arteries and veins. Throughout the experiment, Hartmann's solution was given at a rate of 5 ml/kg/hr. Arterial blood pressure was measured continuously with an electronic pressure transducer. Blood gas and pH were analyzed intermittently by a micro blood gas and pH analyzing system (BMS2 Mk2 blood micro system and PHM72 Mk2 digital acid-base analyzer, Radiometer Ltd., Denmark). The right lingual artery was exposed and a catheter was inserted, so that its tip lay at the junction of this vessel with the carotid artery. This catheter was used for the injection of radioactive (^{85}Kr) dissolved in saline for the measurement of rCBF.

Skin and muscle were reflected from the skull and a trephine hole of 1.5 cm diameter was made over the right parietal cortex. The dura was reflected and the parietal cortical surface was covered with plastic sheeting (Melanex) which was removed intermittently for the application of the oxygen electrode. Two silver discs were attached by adhesive to the skull immediately anterior and posterior to the parietal trephine hole for the recording of one channel of the bipolar EEG (MINGOGRAF 34, ELEMA-SCHÖNANDER, Sweden). The cat's head was mounted in a head holder and the body was positioned prone, with supports under pelvis and upper thorax. The blood pressure transducer was zeroed at the exposed area of the cerebral cortex.

After the surgical preparation was completed, halothane was discontinued and anesthesia was maintained with 0.2 per cent methoxyflurane and 50 per cent nitrous oxide in oxygen throughout the study. The concentration of methoxyflurane in the arterial blood was analyzed by a gas chromatograph (PYE UNICON 104, England).

The rCBF was measured, by following, with a Geiger-Müller tube, the clearance of beta radiation after a 2 min period of ^{85}Kr injection into the right carotid artery. The rCBF was calculated by inserting $T_{1/2}$ (time to half-clearance) in the equation $\text{rCBF} = \frac{\lambda \ln 2}{T_{1/2}}$, where λ is the blood brain partition coefficient of Kr, which was corrected for the measured hematocrit (Ht)⁴⁾.

$$\lambda = 0.92 \cdot \frac{0.843}{\text{Ht}/100 + 0.685 \left(1 - \frac{\text{Ht}}{100}\right)}$$

Pbo_2 was measured with the multi-wire Po_2 electrode described by Leniger - Follert and colleagues⁵⁾. This gave 7 channels of Po_2 from 7 platinum cathodes disposed on the surface of the electrode. The electrode was covered with an inner layer of cellophane (12μ thickness) and an outer membrane of teflon (12μ thickness), and calibration was perfor-

med with zero P_{O_2} solution (Radiometer, Ltd., Denmark) and with air-equilibrated saline, immediately before and immediately after each period of P_{bO_2} measurement. The multi-wire oxygen electrode was mounted in a counter-balanced arm so that the pressure on the brain surface was less than 10 mg distributed over a surface area of 80 mm². The output from each wire was amplified and converted to a digital signal, which was recorded at 0.8 second intervals on a magnetic tape. Subsequently the data was handled by a programmable calculator (WANG 720, U.S.A.), which printed out mean P_{bO_2} values with standard deviations from each cathode for each minute of measurement. These values were corrected by application of the observed calibration drift, assuming linear drift with time.

Following the completion of the surgical preparation, no measurements were made for over one hour, then four control measurements of rCBF and four sets of P_{bO_2} measurements were made under the conditions of normocapnia and normotension. After these control measurements, the cats were randomly divided into two groups of 5 cats each and MAP was reduced to 30-35 mmHg by either SNP or TMP, with 0.2 mg/kg propranolol initially and 0.1 mg/kg following every 30 min. SNP was administered intravenously by an infusion pump and was limited up to 1.0 mg/kg. TMP was infused by the same method, but with a maximum permitted total dose of 10 mg/kg/hr. In most cats in both groups, it was necessary to remove approximately 15 ml of blood to produce the desired levels of hypotension. Thirty minutes after the start of induced hypotension, two rCBF and three sets of P_{bO_2} measurement were made.

Statistical significance was determined by the unpaired student t-test ($P < 0.05$, considered statistically significant).

RESULTS

Table 1 shows the experimental conditions including blood gas, pH

Table 1. Experimental conditions

	MAP mmHg	P_{aO_2} mmHg	P_{aCO_2} mmHg	pH	Hb g/dl	Methoxy- flurane mg/dl	Heart rate beats/min	Temperature °C
Control	106±2	159±2	29±0.3	7.39±0.01	12.1±0.2	11.7±0.7	221±3	38.2±0.0
SNP	33±0*	165±3	29±0.9	7.31±0.02*#	9.2±0.5*	13.7±1.2	178±5*	38.1±0.1
TMP	32±0*	154±5	29±0.8	7.21±0.03*#	9.6±0.4*	12.4±0.6	171±3*	37.9±0.1*

Mean ± SE

* Significantly different from control

Significantly different between sodium nitroprusside (SNP) and trimethaphan (TMP)

values, hemoglobin levels, blood methoxyflurane concentrations, heart rates and rectal temperatures at normotension "control" and during drug-induced hypotension at 32-33 mmHg of MAP. There were no statistically significant differences between P_{aO_2} or P_{aCO_2} values. Both hypotensive groups showed metabolic acidosis which was more severe in the TMP than in the SNP group. Hemoglobin fell by 3.0 and 2.6 g/dl in the SNP and TMP groups, respectively. Rectal temperatures fell 0.3°C in the TMP group. Propranolol significantly reduced the heart rate equally in the two hypotensive groups.

The P_{bO_2} measured at different areas on the surface of the brain cortex under particular circumstances varied widely. In order to represent these results in a comprehensible manner, frequency histograms of P_{bO_2} have been constructed with 10 mmHg class intervals of P_{bO_2} on the x-axis and percentage frequency of observations on the y-axis. Percentage frequency was obtained by dividing the number of measurements made within any class interval of P_{bO_2} by the total number of measurements made in each group. In order to obtain the most secure histogram for "control" the two controls from the SNP and TMP group have therefore been combined. The shaded area in Fig. 1 shows the frequency histogram of P_{bO_2} at normotension, based on 1960 measurements. This formed the "control" histogram for comparison with the values obtained under hypotension. The modal P_{bO_2} values were in a class interval of 30 to 40 mmHg, while mean P_{bO_2} was 51 mmHg. Panel (A) in Fig. 1 shows the frequency histogram of P_{bO_2} , based on 420 measurements at 33 mmHg of MAP during SNP, compared with the "control" shown by the shaded area. The mean P_{bO_2} increased slightly to 54 mmHg but the modal class interval shifted to a lower interval of 20 to 30 mmHg. During hypotension, there might have been a small shift to lower P_{bO_2} values than "control", but in this experiment there was no statistically significant difference between the histograms of "control" and that obtained under SNP. Panel (B) in Fig. 1 shows the frequency histogram of P_{bO_2} , based on 570 measurements at 32 mmHg of MAP during TMP hypotension. When compared with "control", the mean P_{bO_2} decreased to 42 mmHg and the modal P_{bO_2} values fell in a class interval of 10 to 20 mmHg. The TMP histogram was significantly more hypoxic than the one from SNP hypotension. The number of P_{bO_2} measurements less than 10 mmHg under TMP hypotension was significantly greater than the number under SNP hypotension. The frequency histograms of control, SNP and TMP groups converted to a semi-logarithmic presentation with logarithmic intervals of P_{bO_2} on the x-axis is shown in Fig. 2. These demonstrate that the distribution of P_{bO_2} on the cor-

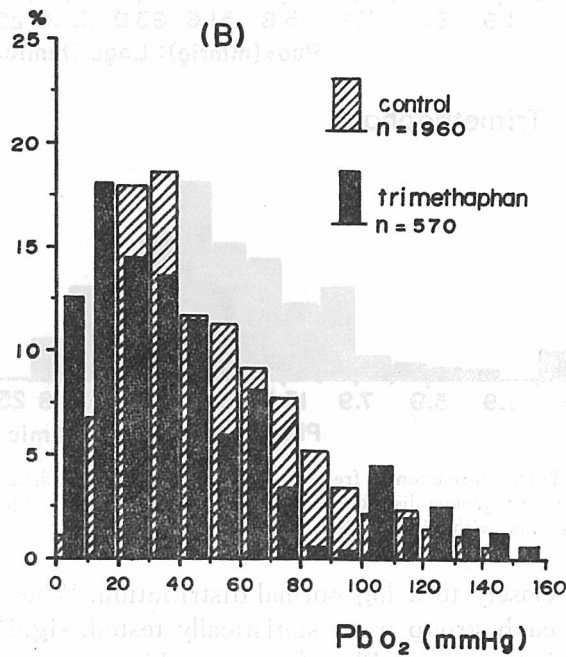
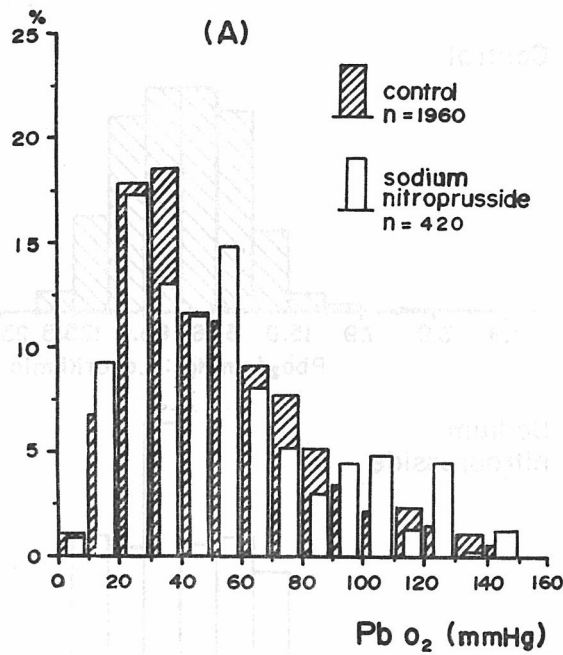


Fig. 1. Frequency histograms of brain surface oxygen tension (PbO₂) during drug-induced hypotension. Shaded area indicates "Control" at normotension (106 ± 2 mmHg). (A); Sodium nitroprusside hypotension (33 ± 0 mmHg) (B); Trimethaphan hypotension (32 ± 0 mmHg).

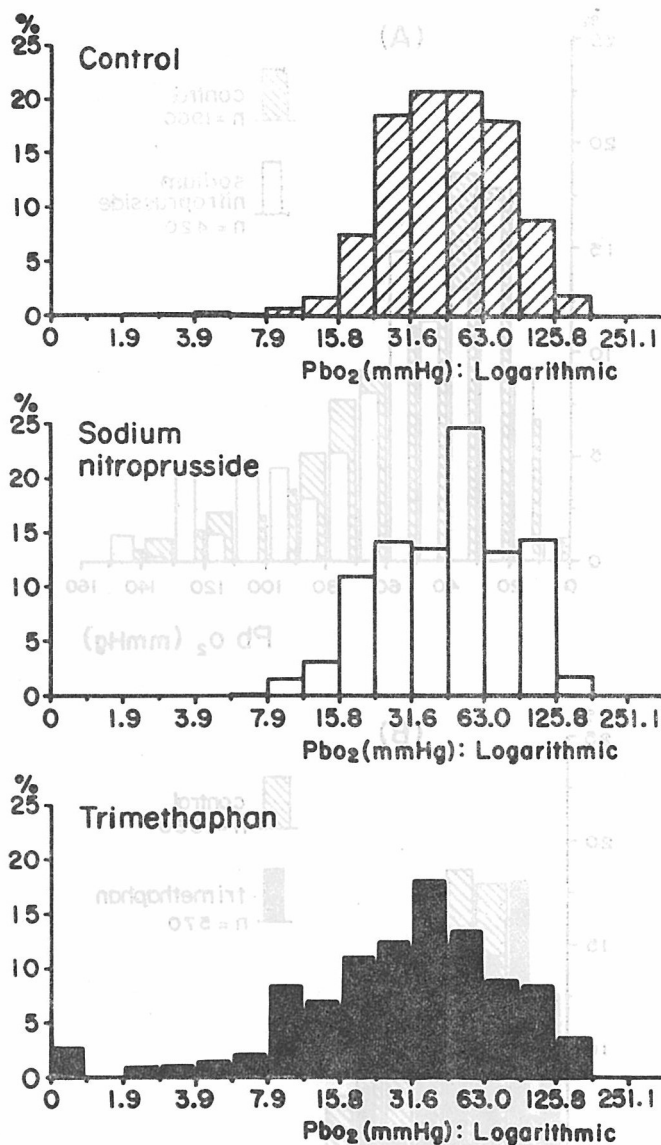


Fig. 2. Logarithmic transformation of frequency distribution during drug-induced hypotension. Frequency distribution with sodium nitroprusside significantly differs from that with trimethaphan.

tical surface fit closely to a log normal distribution. When the log normal distributions in each group were statistically tested, significant differences were found between the P_{bo_2} frequency histograms obtained under TMP hypotension and "control", and between those obtained under TMP and SNP hypotension.

Table 2. Cerebral circulation

	MAP mmHg	rCBF ml/100g/min	CVR mmHg/ml/100g/min
Control	106±2	76±2	1.43±0.05
SNP	33±0*	68±7#	0.49±0.05*#
TMP	32±0*	45±4*#	0.72±0.03*#

Mean ± SE

* Significantly different from control

Significantly different between sodium nitroprusside (SNP) and trimethaphan (TMP)

MAP ; Mean arterial pressure

rCBF ; Regional cerebral blood flow

CVR ; Cerebral vascular resistance

Table 2 shows that rCBF fell to 59 per cent of control at 32 mmHg of MAP during TMP hypotension, but did not fall significantly from control during SNP hypotension. The remarkable autoregulation of flow seen during SNP hypotension was also illustrated by the cerebral vascular resistance (CVR) which fell to 34 per cent of control with SNP, compared with 50 per cent of control during TMP hypotension. There was also a significant difference in CVR between both hypotensive groups.

DISCUSSION

This study clearly indicates that cerebral oxygenation during SNP hypotension was maintained better than during TMP hypotension. The particular multi-wire oxygen electrode used was designed by Leniger-Follert and colleagues⁵⁾ and the shapes of the histograms distributions in the present study are similar to those reported by Lübbers^{6,7)}. Leniger-Follert and her colleagues⁵⁾ reported lower modal P_{bO_2} in cats (25-30 mmHg) than what was found in this study (30-40 mmHg). This discrepancy is probably due to the difference in anesthetic techniques, they used barbiturate which decreased the cerebral blood flow and cerebral metabolic rate for oxygen^{8,9)}, while methoxyflurane and nitrous oxide were used in this study. It is almost certain that cerebral blood flow exceeds oxygen demand during methoxyflurane and nitrous oxide anesthesia^{10,11)}. Despite the difference in modal P_{bO_2} , the shape of the frequency distributions in this study and in Lübbers' work are very similar.

As reported previously by others^{6,12)}, brain surface oxygen tension varied widely from one point on the cortical surface to another. This

variation was due to the geometry of the position of the electrode with respect to surface arteries and veins. The cathode diameter was $15\mu\text{m}$ and it is believed that an oxygen electrode is affected by the oxygen values in a volume of tissue with a diameter approximately the square of the electrode diameter, i.e. $225\mu\text{m}^2$. Therefore, in this study each cathode might have been influenced by several capillary fields, so that the very low values of 1-2 mmHg reported by those^{6,12)} using very fine electrode tips were rarely seen with the electrode used here.

When a logarithmic transformation of the frequency distribution was performed, it revealed that the distribution was a log normal one. This facilitated the statistical comparisons of the frequency histograms obtained under different experimental conditions, and it was found that the histogram of Pbo_2 with SNP significantly differed from that with TMP but not from that of control.

When the MAP was reduced, the modal Pbo_2 value moved downwards but the shape of the Pbo_2 distribution remained log normal, suggesting that homogenous tissue perfusion continued, i.e. there were no areas of no-flow.

Though the number of measurements of rCBF were small, a highly-significant difference was found between rCBF during SNP hypotension, as compared with TMP hypotension. This is in agreement with the findings of Stoyka & Schutz¹³⁾, and Michenfelder & Theye²⁾, and presumably, is sufficient explanation for the well-maintained Pbo_2 values with SNP. The rCBF during hypotension with SNP at 33 mmHg of MAP did not in fact differ significantly from control.

This study was designed to simulate the most extreme degrees of hypotension, and the methods used to induce drug-induced hypotension were chosen to correspond with clinical practice. Since the animals were young and healthy, propranolol was used as it might be fit patients to prevent escape tachycardia¹⁴⁾. Unfortunately but inevitably, some blood had to be removed from the animals in order to achieve the very low MAP sought. The amount of blood removed in the drug-induced groups was small. This blood removal allowed the total dose of SNP to reach within the limit of 1.0 mg/kg/hr, and prevented cyanide toxicity¹⁵⁾.

Hemoglobin levels decreased significantly, indicating hemodilution. Decrease in hemoglobin concentration accompanied by hemodilution during hypotension was well documented in other studies. In the clinical study of Griffiths et al¹⁶⁾, hemoglobin fell by 0.5 g/dl during less severe hypotension produced by SNP, and in Michenfelder & Theye's study in the dog²⁾, hemoglobin fell with all the techniques used to obtain hypo-

tension. The maintenance of the close to control P_{bO_2} pattern during SNP hypotension is even more impressive considering the amount of blood removed and hemodilution.

Michenfelder & Theye²⁾ studied dog made hypotensive by halothane, SNP or TMP down to 40 and 30 mmHg of MAP, at brain level, the latter level being identical to that used here. They found better maintenance of cerebral blood flow with SNP hypotension and also concluded, that at 40 mmHg MAP at brain level, SNP hypotension appears to be superior to that produced by TMP. However, the measurements of brain tissue lactate, lactate/pyruvate ratio, ATP and phosphocreatine revealed equal disturbances at 30 mmHg of MAP with all hypotensive techniques, despite the fact that cerebral blood flow was significantly higher during SNP hypotension. They, therefore, further concluded that at very low perfusion pressures the "deleterious cerebral metabolic effects that occur are unaffected by the technique used for inducing hypotension or by differences in total flow to the brain." The suggestion that the discrepancy between cerebral circulatory and metabolic effects with SNP might be due to uneven local tissue perfusion in the presence of satisfactory overall blood flow, was not supported by their carbon black measurements microflow, and is not supported by the P_{bO_2} measurements reported here, for these refer to localized brain tissue areas.

Another interpretation of Michenfelder & Theye data is possible. The dogs in their study received up to 2.5 mg/kg SNP, but subsequent analysis of their data led them to conclude that doses greater than 1.0 mg/kg were toxic in the dog. When they divided their cerebral metabolic results into those from dogs receiving more than 1 mg/kg and those receiving less, it became clear that when SNP toxicity was avoided, brain lactate and lactate/pyruvate ratios were lower than with TMP hypotension, although ATP and phosphocreatine levels were similar. There is therefore some evidence from their paper that, even at the lowest blood pressures, SNP showed advantages over TMP.

From a different standpoint, Turner and colleagues¹⁷⁾ have shown that at moderate degrees of hypotension (70-90% of prehypotensive blood pressure), SNP increased intracranial pressure (ICP), probably because of expansion of the intracranial blood volume. This might be deleterious in the presence of advanced intracranial compression; also the accompanying increase in brain bulk may result in a deterioration of operating conditions. Thus, SNP seems to have the disadvantage of increasing ICP, but to have the advantage of maintained perfusion and P_{bO_2} at deep hypotension, while TMP does not elevate ICP at modest levels of hypotension¹⁸⁾. Thus, this suggests the possibility of a hypoten-

sive technique which starts with TMP and progresses to SNP for the brief periods of the operation at which extreme hypotension is needed.

SUMMARY

Brain surface oxygen tension (P_{bO_2}) and regional cerebral blood flow (rCBF) were measured during normotension at 106 mmHg and during hypotension at 30-35 mmHg of mean arterial pressure (MAP), using sodium nitroprusside (SNP) or trimethaphan (TMP) in cats anesthetized with methoxyflurane and nitrous oxide. Frequency histograms of P_{bO_2} were constructed during normotension and hypotension. The histogram of P_{bO_2} in the SNP group was not different from the control, whereas in the TMP group there was a prominence of lower values which was significantly different from the SNP group. With SNP, the rCBF and cerebral vascular resistance (CVR) decreased to 89 per cent and 34 per cent of control respectively, while with TMP the rCBF and the CVR decreased significantly to 59 per cent and 50 per cent of control respectively. The rCBF and CVR during SNP were significantly different from those during TMP. These results indicate that the tissue oxygenation of the brain during SNP hypotension was maintained better than during TMP hypotension, and is probably due to the smaller decrease in rCBF during SNP hypotension.

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