

## Cerebral Cortical Extracellular Fluid $H^+$ and $K^+$ Activities during Hypotension in Cats

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Cerebral cortical blood flow, electrical activity, and extracellular fluid (ECF) pH and  $K^+$  ion activities were measured in anesthetized cats (0.7% halothane 65%  $N_2O$  in  $O_2$ ) subjected to hypotension (mean BP 30-32 and 26-28 mmHg), induced by either practolol and trimetaphan (TMP) or practolol and nitroprusside (NTP). Limited blood withdrawal was also necessary to achieve these blood pressure (BP) levels.

Cerebral cortical blood flow during hypotension was greater with NTP than with TMP, and hyperemia occurred in the recovery phase after NTP but not TMP. Electrical activity also was maintained better with NTP. ECF  $K^+$  increased in five of six TMP experiments but in only one of six NTP experiments. Values of  $K^+$  greater than 15 mM were only seen in the TMP group. Release of  $K^+$  into the ECF space occurred at values of cerebral cortical oxygen delivery below 3 ml 100  $g^{-1}min^{-1}$ . ECF  $K^+$  partially recovered after the end of hypotension in all except the experiment with the highest value. A progressive and severe cerebral acidosis was seen in all experiments during induced hypotension, and values below pH 6.50 were present at the stage of  $K^+$  increase in the ECF space. It is concluded that the ability of cell membranes in the cat's cortex to maintain normal ionic gradients is depressed by hypotension to these levels with TMP, but not with NTP, and that this difference is related to better-maintained oxygen supply values during NTP hypotension. (Key words: Anesthetic techniques: hypotension, nitroprusside, trimetaphan. Brain: blood flow; electroencephalogram; pH. Ions:  $K^+$ . Pharmacology: nitroprusside; trimetaphan.)

IN NEUROSURGICAL ANESTHESIA, hypotensive techniques are used to improve intraoperative conditions, particularly for operation on intracranial arterial aneurysms, where a reduction in aneurysm wall tension is required before clipping. Similarly, hypotension will reduce the vascularity of tumors containing abnormal blood vessels in which the flow is pressure dependent. Intravenous agents commonly employed to induce hypotension are sodium nitroprusside (NTP) and trimetaphan (TMP), and these drugs have different effects on the cerebral circulation. Cerebral blood flow (CBF) is

greater during NTP than TMP hypotension,<sup>1,2</sup> and, as a result, cortical surface oxygen tension and cortical electrical activity both are maintained better with NTP.<sup>3,4</sup>

The question remains: Is there a wider margin of blood pressure (BP) reduction available before ischemic dysfunction of the cerebral cortex appears with NTP than with TMP hypotension? Severe ischemia results in anaerobic metabolism with lactate production and failure of cell membranes to maintain normal ionic concentration gradients, so that potassium ( $K^+$ ) leaks out of cells and calcium ( $Ca^{++}$ ) passes in.<sup>5,6</sup> In these experiments, therefore, pH and  $K^+$  ion activities have been measured in the extracellular fluid (ECF) of the cerebral cortex of the cat during hypotension, induced with either NTP or TMP.

### Methods

Thirteen unselected cats of mean weight 2.6 kg (range 2.0-3.95 kg) were studied. Anesthesia was induced in a Plexiglass® cage using nitrous oxide/oxygen ( $N_2/O_2$ ) with halothane 5%. Suxamethonium 75 mg was administered intramuscularly (im) and the trachea was intubated. The animals were ventilated mechanically with a Starling® pump adjusted to produce normocapnia. Anesthesia was maintained with 65%  $N_2O$  in  $O_2$  and halothane, which was administered from a calibrated vaporizer (Dräger Vapor). Up to 2% inspired halothane was used during surgical preparation of the animal and this was reduced to 0.7% for the experiment. Nonsurgical preparation, including electrode implantation, allowed the inspired halothane concentration to be held at 0.7% for at least 2 hours before beginning the measurements. Pancuronium bromide 0.05 mg was given every 30 min by intravenous (iv) injection. Rectal temperature was measured with a thermistor probe (Yellow Springs Instruments) and controlled with the use of electric and warm-water blankets. The femoral artery and vein were cannulated bilaterally, catheters being passed into the abdominal aorta and inferior vena cava, to allow aortic blood pressure measurement (Statham P23 Db transducer), intermittent arterial blood sampling for blood-gas analysis, iv fluid therapy (Ringer's lactate, 5 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>), and drug infusion.

Through an incision below the right ramus of the mandible, the lingual artery was identified deep to the

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diaphragm muscle, and a catheter was passed into this artery until its tip lay at the junction with the carotid artery. This catheter was used later for the infusion of 85-krypton (<sup>85</sup>Kr) dissolved in saline for the measurement of cerebral cortical blood flow.

The animal then was placed in the sphinx position with the head supported in a head holder and with the thorax and abdomen supported on foam rubber. The scalp was incised in the midline and the muscles covering the skull excised. Bilateral parietal burr holes, 1 cm in diameter, were made on the interauricular line, 1 cm either side of the midline. The dura underlying the burr hole on the right side was reflected to expose the underlying cortex, which was covered with a small plastic sheet (Melinex<sup>®</sup>, ICI). A Geiger-Muller tube was positioned over this cortical area in order to count the beta radiation during CBF measurement. For the measurement of cortical CBF, <sup>85</sup>Kr dissolved in saline was injected into the carotid artery at a rate adjusted to maintain a steady level of beta activity in the cortex for 2 min, during which time the <sup>85</sup>Kr equilibrated between blood and brain.<sup>7</sup> The injection then was stopped abruptly and the clearance followed using a Geiger-Muller tube connected to a pulse-height analyzer and analogue amplifier (Panax). The output was recorded on a potentiometric chart recorder. Later, the clearance curve was transferred to semilogarithmic graph paper and the line of best fit obtained, from which time to half-clearance (t<sub>1/2</sub>) was measured. This value was substituted in the equation

$$CBF = \frac{\lambda \log_e 2 \times 60 \times 100 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}}{t_{1/2}}$$

where λ = blood = brain partition coefficient, corrected for the hematocrit existing at the time of flow measurement,<sup>8</sup> t<sub>1/2</sub> = time in seconds to half-clearance of <sup>85</sup>Kr.

On the left side, a small incision was made in the dura of a size sufficient only to allow the implantation of three microelectrodes; one was a K<sup>+</sup>-ion-selective electrode, one a pH electrode, and the third a saline agar-filled reference electrode. The microelectrodes were implanted in the cortical mantle to a depth of up to 500 μm. They were held in micromanipulators and suspended on compliant springs of fine copper wire to allow them to follow brain surface movement. A second reference electrode was implanted in the muscles of the neck. (For further details of electrode construction and calibration see the Appendix.)

Electrical activity of the cortex was measured in the first 10 experiments, using the cerebral function monitor (CFM)<sup>9</sup> connected to two brass screws inserted in the skull immediately anterior and posterior to the site

TABLE 1. Values (Means ± SEM) for BP, CBF, P<sub>aCO<sub>2</sub></sub> and Cortical ECF K<sup>+</sup> for Experiments in Which ECF K<sup>+</sup> Was Measured

	NTP				TMP			
	BP mmHg	CBF ml·100 g <sup>-1</sup> ·min <sup>-1</sup>	P <sub>aCO<sub>2</sub></sub> mmHg	ECF K <sup>+</sup> mM	BP mmHg	CBF ml·100 g <sup>-1</sup> ·min <sup>-1</sup>	P <sub>aCO<sub>2</sub></sub> mmHg	ECF K <sup>+</sup> mM
Normotension (n = 6)	116 ± 8	67 ± 5	33 ± 1	3.3 ± 0.3	104 ± 5	66 ± 6	33 ± 2	3.3 ± 0.3
30 min of hypo- tension to BP 30-32 (n = 6)	32 ± 1	52* ± 8	32* ± 1	4.1 ± 0.4	31 ± 1	27* ± 8	38* ± 2	20.2 ± 7.3
15 min of hypo- tension to BP 26-28 (n = 6)	27 ± 1	53* ± 10	31* ± 2	4.6 ± 0.7	26 ± 1	17* ± 6	38* ± 2	22.4 ± 8.2
Mean values during hypotension at highest ECF K <sup>+</sup> (n = 6)	27 ± 1	53* ± 10	31* ± 2	4.6 † ± 0.7	28 † ± 1	16* ± 5	37* ± 2	26.4 † ± 5.8
Recovery (n = 6)	111 † ± 6	145* ± 30	37 ± 2	3.7 ± 0.1	88 † ± 8	48* ± 7	41 ± 1	21.8 ± 6.6

\* Statistically significant differences between drug groups: Student's *t* test.

† Statistically significant differences between drug groups: Wilcoxon Rank test.

TABLE 2. Values (Means  $\pm$  SEM) for Arterial pH, PaCO<sub>2</sub>, Hb, and Systolic and Diastolic BP for Experiments in Which Cortical ECF K<sup>+</sup> Was Measured

	NTP					TMP				
	pH	PaO <sub>2</sub> mmHg	Hb g/dl	sys BP mmHg	dia BP mmHg	pH	PaO <sub>2</sub> mmHg	Hb g/dl	sys BP mmHg	dia BP mmHg
Normotension (n = 6)	7.32 $\pm$ 0.01	174 $\pm$ 12	12.1 $\pm$ 0.8 n = 5	136 $\pm$ 13	93 $\pm$ 7	7.35 $\pm$ 0.02	177 $\pm$ 5	9.6* $\pm$ 0.7	124 $\pm$ 6	88 $\pm$ 6
30 min of hypotension to BP 30-32 (n = 6)	7.33* $\pm$ 0.01	186 $\pm$ 15	10.0 $\pm$ 0.7 n = 5	39 $\pm$ 1	24 $\pm$ 1	7.21* $\pm$ 0.04	186 $\pm$ 16	8.8 $\pm$ 0.9	43 $\pm$ 2	20 $\pm$ 2
15 min of hypotension to BP 26-28 (n = 6)	7.34 $\pm$ 0.01	190 $\pm$ 14	9.6 $\pm$ 0.7 n = 5	34 $\pm$ 1	20 $\pm$ 1	7.21 $\pm$ 0.07	164 $\pm$ 2	10.4 $\pm$ 1.1	35 $\pm$ 2	17 $\pm$ 2
Mean values during hypotension at highest ECF K <sup>+</sup> (n = 6)	7.34* $\pm$ 0.01	190 $\pm$ 14	9.6 $\pm$ 0.7 n = 5	34 $\pm$ 1	20 $\pm$ 1	7.18* $\pm$ 0.05	188 $\pm$ 14	9.2 $\pm$ 1	39 $\pm$ 3	17 $\pm$ 1
Recovery (n = 6)	7.21 $\pm$ 0.02 n = 5	191 $\pm$ 18 n = 5	11.0 $\pm$ 0.7 n = 4	125 $\pm$ 11	93* $\pm$ 4	7.17 $\pm$ 0.06	188 $\pm$ 11	10.8 $\pm$ 1.2	113 $\pm$ 8	63* $\pm$ 11

\* Statistically significant difference between drug groups: Student's *t* test.

of CBF measurement. In the last three experiments, a six-channel EEG record was made from Ag:AgCl electrodes glued into small drill holes in the skull that penetrated to the inner table and that were located frontally, parietally, and occipitally on each side.

After electrode implantation, the animals were allowed at least 30 min to stabilize before the control measurements. Control values of mean arterial blood pressure (MABP), regional cerebral blood flow (rCBF), cortical ECF pH, and K<sup>+</sup> and electrical activity were measured on three or more occasions in each animal before the induction of hypotension.

Hypotension was induced by a combination of beta blockade, limited blood removal, and either NTP or TMP. Practolol 0.2 mg · kg<sup>-1</sup> was given iv first and then the animals were divided into two groups, with the use of a sequence of random numbers; one group of seven cats received an NTP infusion up to a maximum dose of 1 mg · kg<sup>-1</sup> and the other group of six cats received TMP to a maximum dose of 10 mg · kg<sup>-1</sup> in each case with the use of a syringe pump (Harvard Instruments). BP was lowered at a rate not exceeding 5 mmHg · min<sup>-1</sup> to a mean BP (mBP) of 30-32 mmHg. This level of mBP then was maintained for 30 min, and the BP then was reduced further to an mBP of 26-28 mmHg for 15 min, following which the mBP was allowed to recover. To achieve these levels of hypotension, it was necessary to withdraw blood once the maximum rate of hypotensive drug infusion had been established. The mean volumes of blood removed in the two groups were similar (NTP group—blood removal 11.4  $\pm$  2.2 ml · kg<sup>-1</sup>, TMP group—blood removal 13.7  $\pm$  3.7 ml · kg<sup>-1</sup>).

Measurements of mBP, rCBF, brain ECF K<sup>+</sup>, and pH and electrical activity were made at the end of the initial 30-min period of hypotension to mBP 30-32 mmHg and again at the end of a further 15-min period of hypotension at mBP of 26-28 mmHg. The hypotensive drug infusion then was discontinued, and blood that had been withdrawn was reinfused before final measurements were made. At the time of each flow measurement, arterial blood samples were taken for the measurement of pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, and Hb.

For technical reasons, it was not possible to measure ECF pH and K<sup>+</sup> ion activities in all experiments. Of the seven NTP experiments, simultaneous measurements of ECF K<sup>+</sup> and pH were made in three, ECF K<sup>+</sup> alone was measured in three, and ECF pH alone was measured in one. In the TMP group, measurements of both ECF K<sup>+</sup> and pH were made in four experiments and ECF K<sup>+</sup> alone was measured in two.

Separate means and standard errors were calculated for all subgroups, and differences between the drug groups were tested by the Student's *t* test or the Wil-

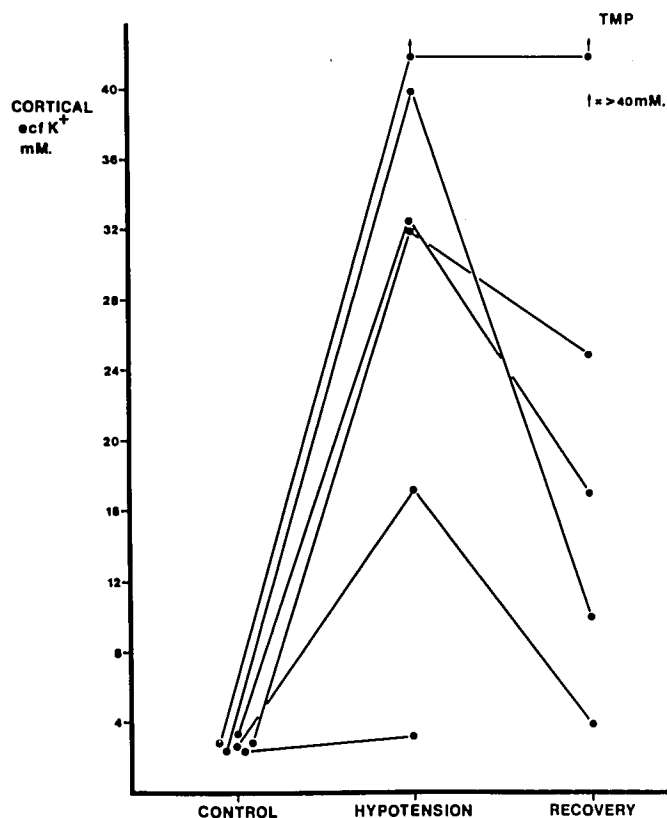


FIG. 1. Values for ECF K<sup>+</sup> during the control, hypotensive, and recovery periods in the animals receiving trimetaphan. The hypotensive value shown for each experiment is the highest recorded during hypotension. The value marked with the arrow indicates a value greater than 40 mM.

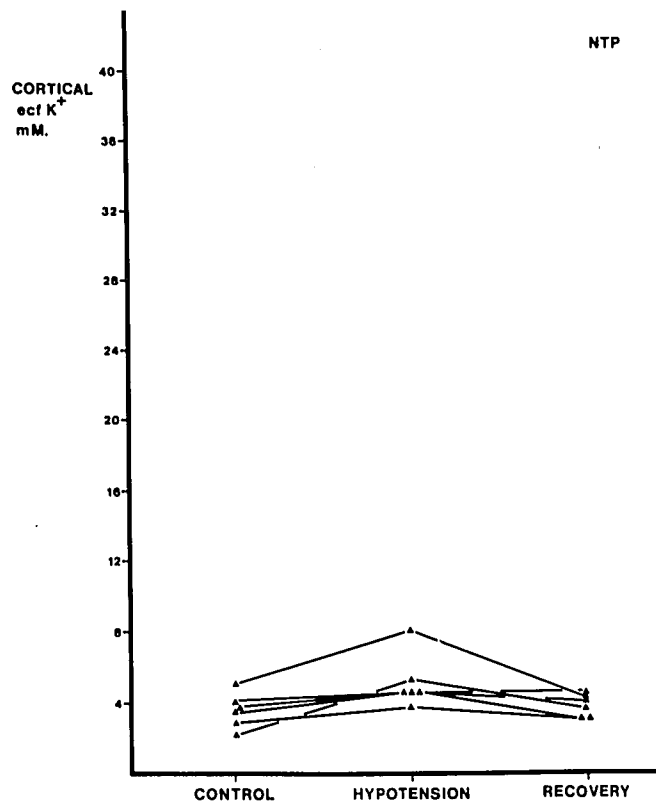


FIG. 2. Values for ECF K<sup>+</sup> during the control, hypotensive, and recovery periods in the animals receiving nitroprusside. The hypotensive value shown for each experiment is the highest recorded during hypotension.

coxon Rank Sum test, as appropriate. *P* values less than 0.05 were considered to be significant. In the case of ECF K<sup>+</sup> values during hypotension, these clearly were distributed not normally, in that the values either were in the normal range or else were increased greatly; the Student's *t* test, therefore, could not be applied and only the Wilcoxon Rank Sum test was used.

### Results

#### ECF K<sup>+</sup> MEASUREMENTS

ECF K<sup>+</sup> was measured in 12 experiments, six with TMP and six with NTP (tables 1 and 2). During the control period there was no significant difference between the groups with respect either to BP, CBF, ECF K<sup>+</sup>, arterial pH, PaO<sub>2</sub>, or PaCO<sub>2</sub>. However, although the

TABLE 3. Values (Means ± SEM) for BP, CBF, PaCO<sub>2</sub>, and Cortical ECF pH for Experiments in Which ECF pH Was Measured. The Hypotension Measurements Given Were Those Obtained at the Lowest pH Observed during Hypotension

	NTP					TMP			
	BP mmHg	CBF ml · 100 g <sup>-1</sup> · min <sup>-1</sup>	PaCO <sub>2</sub> mmHg	ECF pH		BP mmHg	CBF ml · 100 g <sup>-1</sup> · min <sup>-1</sup>	PaCO <sub>2</sub> mmHg	ECF pH
Normotension (n = 4)	117 ± 8	65 ± 3	32 ± 1	7.16 ± 0.02	Normotension (n = 4)	110 ± 1	69 ± 10	34 ± 1	7.21 ± 0.05
Hypotension (n = 4)	27 ± 1	61*† ± 9	31*† ± 2	6.55† ± 0.18	Hypotension (n = 4)	28 ± 2	12*† ± 7	39*† ± 2	5.85† ± 0.15
Recovery (n = 4)	111 ± 11	117*† ± 21	33*† ± 2	6.83 ± 0.21	Recovery (n = 4)	93 ± 8	43*† ± 6	41*† ± 1	6.37 ± 0.28

\* Statistically significant difference between drug groups: Wilcoxon Rank test.

† Statistically significant difference between drug groups: Student's *t* test.

TABLE 4. Values (Means  $\pm$  SEM) for Arterial  $pH$ ,  $P_{a_{O_2}}$ , Hb, and Systolic and Diastolic BP for Experiments in Which Cortical  $pH$  Was Measured. The Hypotensive Measurements Given Are Those Obtained at the Lowest  $pH$  Observed during Hypotension. No Statistically Significant Differences Exist Between the Drug Groups

	NTP					TMP				
	$pH$	$P_{a_{O_2}}$ mmHg	Hb g/dl	sys BP mmHg	dia BP mmHg	$pH$	$P_{a_{O_2}}$ mmHg	Hb g/dl	sys BP mmHg	dia BP mmHg
Normo- tension (n = 4)	7.34 $\pm$ 0.03	181 $\pm$ 19	11.9 $\pm$ 16 n = 3	145 $\pm$ 6	90 $\pm$ 6	7.37 $\pm$ 0.02	182 $\pm$ 5	10.2 $\pm$ 1.0	132 $\pm$ 3	95 $\pm$ 6
Hypo- tension (n = 4)	7.34 $\pm$ 0.01	208 $\pm$ 13	9.4 $\pm$ 1.1 n = 3	33 $\pm$ 1	19 $\pm$ 1	7.22 $\pm$ 0.07	179 $\pm$ 14	9.2 $\pm$ 1.3	38 $\pm$ 4	17 $\pm$ 2
Recovery (n = 4)	7.22 $\pm$ 0.05 n = 3	216 $\pm$ 20 n = 3	11.7 $\pm$ 0.4 n = 3	127 $\pm$ 18	89 $\pm$ 8	7.21 $\pm$ 0.05	190 $\pm$ 8	11.9 $\pm$ 0.9	118 $\pm$ 8	68 $\pm$ 11

experiments were done in random order, there was a significant difference in Hb levels between the groups, with the NTP animals having a greater value than the TMP ones.

With the induction of hypotension, CBF was significantly greater at BP levels of both 30–32 and 26–28 mmHg in the NTP group, as compared with the TMP group, despite a slight but significantly greater  $P_{a_{CO_2}}$  in the latter. During hypotension there was no significant difference in the Hb values between the drug groups.

ECF  $K^+$  increased significantly during hypotension in the animals receiving TMP but not in those rendered hypotensive with NTP. ECF  $K^+$  increased to 15 mM or above in five of six TMP experiments (fig. 1), while only one animal showed an increase during NTP hypotension and that was to 8.1 mM (fig. 2). In three TMP experiments the increases in ECF  $K^+$  occurred at BP 30–32 mmHg and in the other two at 26–28 mmHg. The single increase with NTP first occurred at BP 30–32 mmHg. There was no difference in Hb values between the groups at the time of the highest ECF  $K^+$  measurement.

When the BP was allowed to recover, CBF increased to hyperemic values in the NTP group but was less than control values in the TMP animals. In all except one TMP animal, there was some return of ECF  $K^+$  toward control values after the restoration of BP.

#### ECF $pH$ EXPERIMENTS

In the eight animals in which ECF  $pH$  was measured, four in each drug group, a progressive acidosis was observed throughout the duration of hypotension with either drug (tables 3 and 4). The degree of acidosis was significantly more severe in the TMP group, but this was, in part, a result of a greater  $P_{a_{CO_2}}$  value. CBF was significantly less in the TMP group than in the NTP group. There was a partial restitution of ECF  $pH$  in all animals after discontinuation of hypotension.

#### COMBINED MEASUREMENTS

There were 16 simultaneous measurements of ECF  $pH$  and  $K^+$  during hypotension. These values have been plotted in figure 3, from which it will be seen that the release of  $K^+$  into the ECF was associated with ECF  $pH$  values below 6.50.

#### CHANGES IN ELECTRICAL ACTIVITY

Derangements of brain electrical activity were more severe in the TMP group (tables 5 and 6). In two TMP animals, the voltage level in the cerebral function monitor (CFM) decreased 15 and 20 min before the release of ECF  $K^+$  into the extracellular space, and in one an-

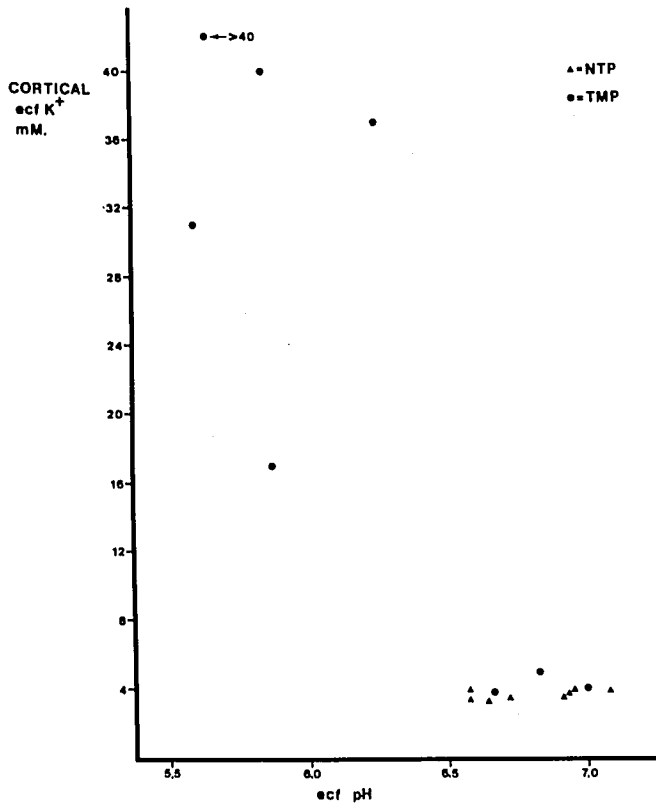


FIG. 3. All simultaneous measurements made of ECF pH and ECF K<sup>+</sup> during drug-induced hypotension.

imal an isoelectric EEG was seen before K<sup>+</sup> release. In one other animal, the voltage level of the CFM decreased at the same time the release of K<sup>+</sup> occurred. One animal exhibited 2–3 s periods of isoelectric EEG with no change in K<sup>+</sup> and one other showed a moderate increase in ECF K<sup>+</sup> with no change in the CFM voltage level. Of the NTP animals, most showed no change in CFM voltage level, but one had some increase in CFM voltage. In the only NTP experiment in which ECF K<sup>+</sup> increased, there was large-amplitude slow-wave activity in the EEG.

### Discussion

The implanted microelectrodes used in this study measure pH and K<sup>+</sup>-ion activities of the ECF within the cerebral cortex. The increases in ECF K<sup>+</sup> seen in some of these experiments represent the failure of neuronal and glial cell membrane function as a result of ischemia, with consequent leakage of K<sup>+</sup> from intracellular to extracellular space. These experiments have demonstrated that ischemia of a degree sufficient to impair membrane function occurs more commonly in the cat during hypotension induced with practolol–trimetaphan than with practolol–nitroprusside, combined in

TABLE 5. Changes in Electrical Activity Compared With Changes in ECF K<sup>+</sup> in NTP Experiments

Experiment Number	Electrical Activity	ECF K <sup>+</sup>
1	No record	No change
2	CFM—no change	No change
3	CFM—increase in total voltage	No change
4	CFM—no change	Increase from 3.3 to 4.5 mM
5	CFM—no change	Increase from 3.0 to 3.7 mM
6	EEG—large amplitude slow activity	8.1 mM

both groups with moderate blood withdrawal. In this respect these findings confirm and extend observations made previously of better-maintained cerebral cortical perfusion during NTP-induced hypotension.<sup>1–3</sup>

The rise in ECF K<sup>+</sup> during incomplete ischemia occurs in three phases: first, a progressive slow increase over several minutes to values of 13–15 mM (phase I); then a very rapid increase to much higher values (phase II); followed by a final slow increase to peak values of 60–75 mM.<sup>5</sup> Experiments by Harris and colleagues,<sup>5</sup> with Ca<sup>++</sup>-selective microelectrodes have shown that Ca<sup>++</sup> movement into the cell occurs at the point of transition from slow to rapid K<sup>+</sup> release, *i.e.*, at about 15 mM ECF K<sup>+</sup>. None of the NTP animals had K<sup>+</sup> changes large enough to suggest Ca<sup>++</sup>-ion shifts, because the highest ECF K<sup>+</sup> measured was 8.1 mM. On the other hand, four of the six TMP animals had K<sup>+</sup> values in excess of 15 mM.

In this study, K<sup>+</sup> release occurred at flow values below 30 ml · 100 g 10 g · min<sup>-1</sup> (fig. 4) and at O<sub>2</sub> delivery

TABLE 6. Changes in Electrical Activity Compared With Changes in ECF K<sup>+</sup> in TMP Experiments

Experiment Number	Electrical Activity	ECF K <sup>+</sup>
1	CFM fall at same time as K <sup>+</sup> increase.	37 mM
2	CFM fall preceded K <sup>+</sup> increase by 15 min.	31 mM
3	CFM no change in level.	15 mM
4	CFM fall preceded K <sup>+</sup> increase by 20 min.	40+ mM
5	EEG isoelectric periods of 2–3 s.	No change
6	Isoelectric EEG preceded K <sup>+</sup> increase by no more than 13 min.	32 mM

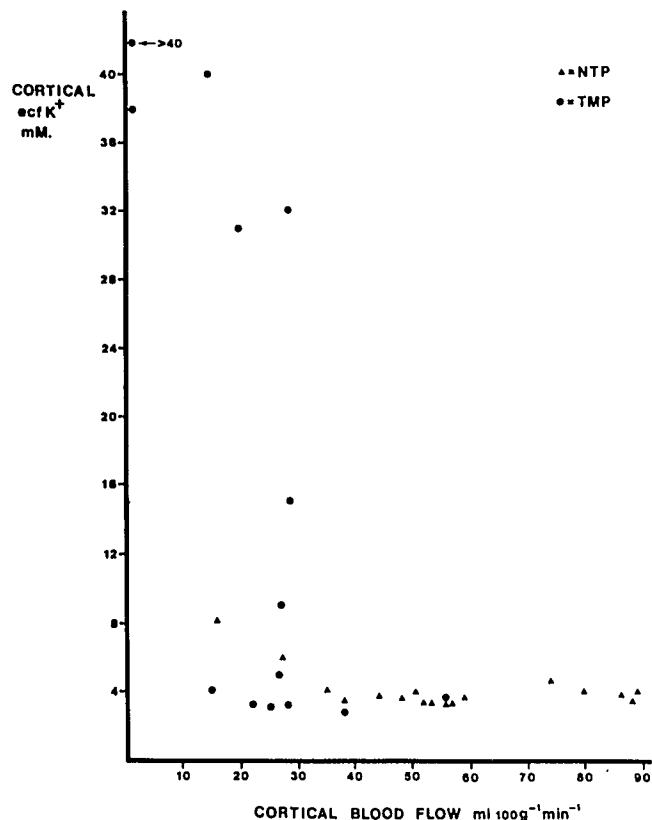


FIG. 4. Cerebral cortical blood flow during hypotension plotted against ECF K<sup>+</sup>.

values below  $3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  ( $\text{O}_2$  delivery = cortical blood flow  $\times$  arterial oxygen content) (fig. 5). Above  $3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  only one abnormal ECF K<sup>+</sup> occurred, while below this value of cortical oxygen delivery there was only one normal value of ECF K<sup>+</sup>.

The cortical acidosis in the TMP animals is readily explained, because the ischemic flow values recorded would give rise to lactic acid production and CO<sub>2</sub> retention. However, an acidosis also was seen in the NTP animals, although mean rCBF was  $55 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ , which should have been adequate to prevent anaerobic glycolysis. Furthermore, adequate cortical P<sub>O<sub>2</sub></sub> values have been demonstrated during NTP hypotension to this level.<sup>3</sup> The possibility of enzyme poisoning by cyanide, causing a failure of oxygen utilization, has to be considered, even though the maximum permitted dose of NTP was  $1 \text{ mg} \cdot \text{kg}^{-1}$ . The limited blood removal employed in these experiments for the control of BP may also have contributed to the ECF acidosis, because Michenfelder and Theye<sup>2</sup> have demonstrated that severe cortical lactic acidosis occurs during oligemic hypotension. This factor would have influenced both groups equally.

The severity of the acidosis, particularly in the TMP

animals, is surprising at first sight, because values as low as 5.60 were recorded. However, partial ischemia is known to produce a more severe acidosis than total ischemia,<sup>10</sup> because of the continuing supply of glucose via the residual blood flow.<sup>11</sup> This acidosis is further accentuated when hyperglycemia is present during cerebral ischemia.<sup>12</sup> Blood glucose was measured in eight of the 13 experiments reported here, and in all cases elevated values of glucose were found during induced hypotension. (Blood glucose in control period— $7.40 \pm \text{SE } 1.30 \text{ mM}$ ,  $n = 8$ , and during hypotension =  $14.80 \pm 1.0 \text{ mM}$ ,  $n = 14$ .) It must also be noted that the significantly greater PaCO<sub>2</sub> in the TMP animals during hypotension would aggravate any existing cortical acidosis and thus reinforce the difference in cortical ECF pH observed between the two groups. However, the modest elevation of PaCO<sub>2</sub> in the TMP group would not have altered cerebral cortical perfusion at this level of BP.<sup>13</sup>

The level of induced hypotension studied in these experiments was low, average systolic pressures being between 34 and 43 mmHg (table 2). However, such levels of BP are used in clinical practice<sup>14</sup> and are also seen if sudden blood loss occurs during induced hypotension.

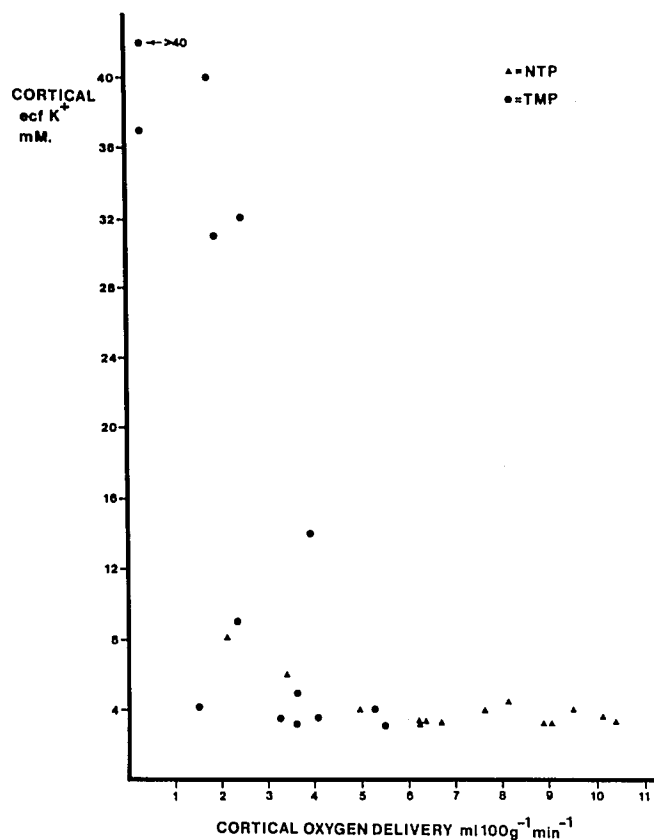


FIG. 5. Cerebral cortical oxygen delivery during hypotension plotted against ECF K<sup>+</sup>.

Routine monitoring for detection of cerebral ischemia in clinical situations such as induced hypotension cannot include measurement of ECF K<sup>+</sup> or pH at the present time. The relationship of changes in these ion activities to depression of electrical activity is important, therefore. Astrup and colleagues<sup>6</sup> have demonstrated that in regional ischemia there is a range of reduced CBF within which the EEG is isoelectric, but there is no leakage of K<sup>+</sup> from intracellular to extracellular space—this they have termed the penumbra of cerebral perfusion. Therefore, the threshold of CBF for electrical silence is greater than the threshold for cell membrane failure. In the NTP experiments reported here, CFM activity either remained unchanged or increased. In the one NTP experiment in which ECF K<sup>+</sup> increased, EEG activity, though abnormal, still was present, but the degree of K<sup>+</sup> increase was, as already noted, well below the 15 mM at which ECF K<sup>+</sup> rises steeply and ECF Ca<sup>++</sup> falls. In the TMP experiments, all four animals with increases of ECF K<sup>+</sup> above 15 mM demonstrated decreases of CFM activity or an isoelectric EEG, which in three cases preceded the K<sup>+</sup> release. It is interesting that in the one experiment in which ECF K<sup>+</sup> reached only 15 mM, the CFM showed no decrease in voltage levels. The experiment in which the EEG contained 2–3 s of burst suppression in the presence of a normal ECF K<sup>+</sup> represents a situation in which cerebral perfusion is in the penumbra range, *i.e.*, below the level to maintain electrical activity but above the value for K<sup>+</sup> release from the cells.

### Conclusion

These experiments appear to offer evidence that ischemic failure of cell membrane function in the cerebral cortex occurs at greater BP levels during TMP, as compared with NTP, hypotension.

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### APPENDIX

#### *Electrode construction and calibration*

Cortical ECF pH was measured with glass microelectrodes of tip diameter less than 10 μm, which were constructed using a modification of the technique described by Gebert.<sup>15</sup> Tubes of H<sup>+</sup> selective glass (Corning 0150) were drawn in an electrode puller into capillaries with tip diameters of 1–10 μm. Such a capillary was then fitted closely inside a larger lead glass capillary so that the pH sensitive glass protruded approximately 25–50 μm beyond the end of the lead glass. The assembled capillaries then were heated gently in a microforge, and viewed through a horizontal stereo microscope so that the lead glass melted onto the pH-sensitive glass to form a seal. The tip of the pH-sensitive glass then was heated further until the end was seen to be sealed. The pH glass capillary then was broken off inside the lead glass above the seal and, when cool, the electrode was filled with 0.1 N HCl buffered to pH 7.0 with 0.3 M tris buffer. A chlorided silver wire (Ag:AgCl) was inserted and the electrode finally sealed with dental wax.

The K<sup>+</sup> ion-selective electrodes consisted of borosilicate glass tubes of 1-mm internal diameter drawn into capillaries with tips of approx 1 μm diameter, and, following siliconization by exposing the open ends of the tubes to dimethylsiloxane vapor, the tips were filled for approximately 500 μm with K<sup>+</sup> selective ion exchange resin (Corning, code 477317). The



tube was then filled from the wider end with 0.5M KCl, using a long, fine capillary, all bubbles being excluded. An Ag:AgCl wire was inserted into the electrode and held in place with dental wax, the end of the tube being left open.

The cortical microreference electrode consisted of a borosilicate glass tube drawn to a tip diameter of about 2  $\mu\text{m}$  and filled with physiologic saline solution in 2% Agar into which an Ag:AgCl wire was sealed. Another reference electrode of similar construction of 20  $\mu\text{m}$  diameter was implanted in the neck muscles of the animal and the outputs of the ion-selective microelectrodes and of the two reference electrodes compared differentially in order to observe changes in the DC potential of the brain. Before implantation, the potential difference between the reference electrodes was measured with

both electrodes in physiologic saline, and they were deemed satisfactory if a stable potential difference of less than 500  $\mu\text{v}$  was recorded over several hours. The outputs of the ion-selective electrodes were amplified differentially against the two reference electrodes so that changes in DC potential of the brain did not influence the observed values for  $\text{K}^+$  and  $\text{pH}$ . DC differential amplifiers with a high input impedance ( $>10^{13}\Omega$ ) were employed.

Calibration of the  $\text{pH}$  electrodes was carried out using appropriate buffers<sup>16</sup> and calibration of the  $\text{K}^+$  electrodes was carried out with solutions of KCl in sodium chloride, with  $\text{K}^+$  concentrations of 1, 3, 5, 8, 10, 20, and 40 mM and the chloride ion ( $\text{Cl}^-$ ) concentration held at 150 mM, the cationic balance being maintained at 150 mM by  $\text{Na}^+$ .