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Cerebral Blood Flow, Circulation, and Blood Homeostasis of Dogs During Slow Cyanide Poisoning and After Treatment with 4-Dimethylaminophenol

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Abstract. The effects of 4-dimethylaminophenol · HCl (DMAP) and 100% oxygen on cerebral blood flow (CBF) and peripheral circulation, arterial and venous blood gases, and other parameters have been investigated in dogs in the course of slow cyanide infusion.

The i.v. infusion of KCN increased the respiratory minute volume, accompanied by a rise in arterial pO_2 and pH and a decrease in arterial pCO_2 while the venous lactate concentration increased by about 500% and the hemoglobin content and hematocrit by about 30%. Heart rate and carotid artery blood flow decreased. Local CBF in the cingulum as measured with thermocouples rose steadily, and the brain and oesophagus temperature were lowered. The breathing of 100% oxygen raised the local CBF, the temperature, and the arterial pCO_2.

During the infusion of KCN into the femoral artery of artificially ventilated dogs the femoral venous pO_2 increased continuously by some 40 mm Hg, attended with a decrease in pCO_2 of 15 mm Hg. The femoral blood flow, however, rose sharply within 3 min. 100% oxygen induced a rise in pCO_2 and a diminution of pH in the femoral vein and in the sinus sagittalis, and the femoral flow rose rapidly.

After DMAP i.v. the values of most of the parameters returned to normal or finally stabilized below or above the initial level. The rise in the hemoglobin content, hematocrit, and lactate concentration was stopped, but the arterial and venous pH remained or were lowered. DMAP elicited a rapid, strong decrease in the pO_2 of the femoral vein and the sinus sagittalis with a concomitant marked increase in pCO_2.

Key words: 4-Dimethylaminophenol – Oxygen – Cyanide poisoning – Cerebral blood flow

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Introduction

The response of cerebral blood flow (CBF), peripheral blood flow, and blood gases during poisoning by cyanide and after the administration of an antidote in the absence or in the presence of cyanide is of significance for a reasonable evaluation of antidotal therapy that takes into account the demand for oxygen in the tissues. The present study has been undertaken to investigate the corresponding effects of the cyanide antidote 4-dimethylaminophenol · HCl (DMAP) in the course of slow cyanide poisoning, that is demonstrable in a simple way by the infusion of cyanide. For the administration of cyanide KCN has been chosen at a rate of 0.072 mg $kg^{-1} \cdot min^{-1}$ for which the pharmacokinetics is known from a study of Christel et al. (1977), who observed respiratory arrest when the concentration of cyanide in the blood plasma reached 40 µmol/l, with 60% being bound to plasma proteins. The rate of infusion is only slightly different from that used in two studies dealing with the circulation, respiration, and O_2 saturation in cyanide-poisoned dogs (0.08 mg $kg^{-1} \cdot min^{-1}$; Mercker et al. 1958) and the treatment with specific antidotes (Mercker and Roser 1957) so that a comparison of the corresponding results is possible. The effects on CBF and blood-gases due to DMAP alone, whose great detoxifying capacity has been demonstrated by measuring the HCN exhaled by cyanide-poisoned cats (Schwarzkopf and Friedberg 1971), have recently been reported elsewhere (Klimmek et al. 1981).

Materials and Methods

Male beagle dogs weighing 12.5 ± 0.4 kg (mean ± SE) were anesthetized with thiopental-Na (10 mg/kg i.v.) and chloralose (α-D(+)-gluco-chloralose, dissolved in propanediol-1,2, 50 mg/kg i.v.). Administration of the anesthetic was repeated as required. After tracheal intubation most of the dogs were allowed to breathe spontaneously; part of them was ventilated with room air by a Schuler respirator (Braun-Melsungen) during relaxation with alcuronium. Half of the initial dose of alcuronium (0.04 mg/kg i.v.) was administered at 20 min intervals.

Except the experiments which included the use of thermocouples, clotting of the blood was prevented by heparin (500 U.S.P.-U/kg i.v.) whose administration was repeated every hour (250 U.S.P.-U/kg i.v.).

Lactate was measured with Biochemica-Test-Combinations (Boehringer, Mannheim, FRG) by the reaction with lactate dehydrogenase. Hemoglobin was determined at 546 nm against a standard solution of ferrihemoglobin cyanide (Van Kampen and Zijlstra 1961), hematocrit by centrifugation of blood samples taken in microtubes.

The dogs lay in a hanging device. The muzzle was fastened by a leather band on a molded metal plate, and the head was held by two bars from both sides on the level of the ears. A hole was drilled in the crista sagittalis to admit the insertion of a tube into the sinus sagittalis. Sinus sagittalis and jugular vein were connected with each other by an anastomosis in which the flow was measured with electromagnetic flow probes (Hellige), that were also used in the carotid artery or femoral vein. Blood pressure was recorded with Statham transducers connected to the femoral artery. Heart rate was derived from the ECG by a frequency gauge, respiratory minute volume was measured with a pneumotachometer.

PO_2, pCO_2, and pH of the blood were determined continuously with a micro blood-gas analyzer (Gas Check AVL) in the femoral artery, femoral vein, carotid artery or sinus sagittalis. For this purpose, the arterial or venous blood was pumped through the measuring chamber of the analyzer and returned to the corresponding venous vessel.

Local cerebral blood flow (CBF) was determined with thermocouples according to Hensel (1961), who has modified the needle flow recorder derived by Gibbs (1933). The thermocouple unit was produced by Hartmann & Braun, Frankfurt/M, FRG. The scalp was dissected over the crista sagittalis, and the tissue was removed from the skull on both sides of the sagittal suture. On the right hemisphere, before the protuberantia occipitalis externa and 0.5 cm beside the sagittal suture, two channels of 1 mm in diameter and 1.3 cm in distance were bored vertically in the skull. The tips of the thermocouple cannulas were inserted into the bore holes and pushed forward by 1.5 cm through the gyrus marginalis before being stopped in the cingulum. In a similar manner another thermocouple was inserted into the left hemisphere for measurements of the absolute brain temperature.

Bleeding in the skull was prevented by a powder mixture containing $FeCl_3$, dichlorophen and thrombin (Thrombo-Tuffon).

The absolute temperature and the temperature difference between the heated and unheated thermojunctions were recorded by the Fluvograph 2 (Hartmann & Braun, Frankfurt/M, FRG).

From the temperature difference δ the heat conductivity λ was calculated by the formula $\lambda = K_1 \cdot I^2/\delta - K_2$. The intensity of the current I was adjusted to 13 mA, resulting in a temperature difference of 2° C between the thermojunctions. The resolving power of the potentiometer was 0.02° C.

λ_{100} denotes the heat conductivity of the living anesthetized brain before any treatment. For the determination of λ_0, the heat conductivity of the dead brain, the animals had to be sacrificed. The brain was removed, and a cubic piece of about 2 cm in length was cut out from the cingulum tissue. The brain tissue was stored in 0.9% NaCl solution under room air and equilibrated in a water bath of 37° C. λ_0 was determined in the same manner as described above.

$\Delta\lambda_{100}$ equals the difference between λ_{100} and λ_0 and is a parameter for the local resting blood flow in the brain. For graphic representation each change $\Delta\lambda$ at any time is related to $\Delta\lambda_{100}$. Thus, the percent change in the resting heat conductivity $\Delta\lambda_{100}$ is obtained as measure for the change in local cerebral blood flow.

The data are presented as arithmetic means ± standard error (SE). Significance was estimated on a 5% level with Student's paired *t*-test.

Results

Experiments During Spontaneous Respiration

Because respiratory arrest occurred at very different times between 35 and 55 min after the beginning of the cyanide infusion, the values of the various parameters recorded as analog data were averaged by starting from the time of DMAP injection ($t = 0$) in both directions. DMAP was always given intravenously 1 min after the last respiration.

During the infusion of cyanide heart rate (Fig. 1) decreased by about 40% from 170.6 ± 6.2 to 102.2 ± 16.1/min and carotid artery blood flow (Fig. 1) decreased by about 64% from 103.4 ± 18.7 to 37 ± 9.8 ml/min at respiratory arrest. The values normalized or returned to higher levels within 10 min after injection of DMAP.

Mean arterial pressure (Fig. 1) diminished in the first 20 min from 149.7 ± 6.7 to 132.2 ± 7.9 mm Hg; together with the systolic and diastolic pressure it began to rise rapidly 10 min before respiratory arrest occurred. DMAP enhanced the systolic and/or diastolic increase in blood pressure for 2–3 min followed by a fall below the pre-infusion level.

Within 20 min, respiratory minute volume (Fig. 1) increased by about 58% from 11.5 ± 2 to 18.2 ± 1.6 l/min while pO_2 and pH (Fig. 2) were rising from

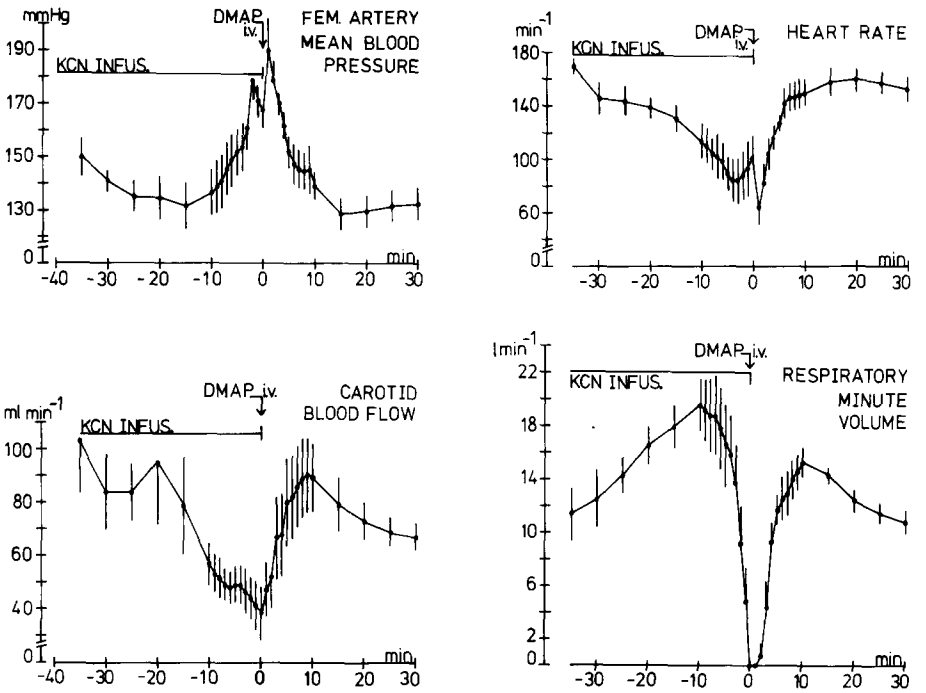

Fig. 1. Mean arterial pressure ($n = 6$), heart rate ($n = 6$), carotid artery blood flow ($n = 5$), and respiratory minute volume ($n = 5$) of chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$ i.v.). Effect of DMAP (3.25 mg/kg i.v.) together with the discontinuation of the infusion 1 min after respiratory arrest. Means ± SE

87.3 ± 5.7 to 98.3 ± 6.7 mm Hg and from 7.32 ± 0.02 to 7.45 ± 0.01, respectively. Simultaneously, pCO_2 (Fig. 2) decreased from 37 ± 4 to 22.5 ± 1.3 mm Hg. Ten minutes before respiratory arrest, respiratory minute volume and pH began to decrease while pO_2 and pCO_2 continued to rise and to fall, respectively. DMAP induced an increase in arterial pCO_2 from 12.2 ± 0.8 to 28 ± 6.4 mm Hg within 10 min, accompanied by a further diminution of pH to 6.8 ± 0.07 and a decrease in pO_2 below the pre-infusion level (Fig. 2).

At the time of respiratory arrest, the venous lactate concentration had increased by about 500%, the hemoglobin content and the hematocrit by about 30%. They did not continue to increase after injection of DMAP (Fig. 3). Unlike the analog data the values of these parameters could not be averaged on account of their discrete determination.

The heat conductivity in the cingulum (Fig. 4) increased by 45.3 ± 14% before respiratory arrest. DMAP produced an additional rise in heat conductivity to 73.5 ± 11% above the baseline level within 7 min. Then the heat conductivity returned to normal. The brain temperature (Fig. 4) diminished by 0.4 ± 0.14° C during the cyanide infusion. It rose transiently by 0.21 ± 0.05° C within 6 min after injection of DMAP.

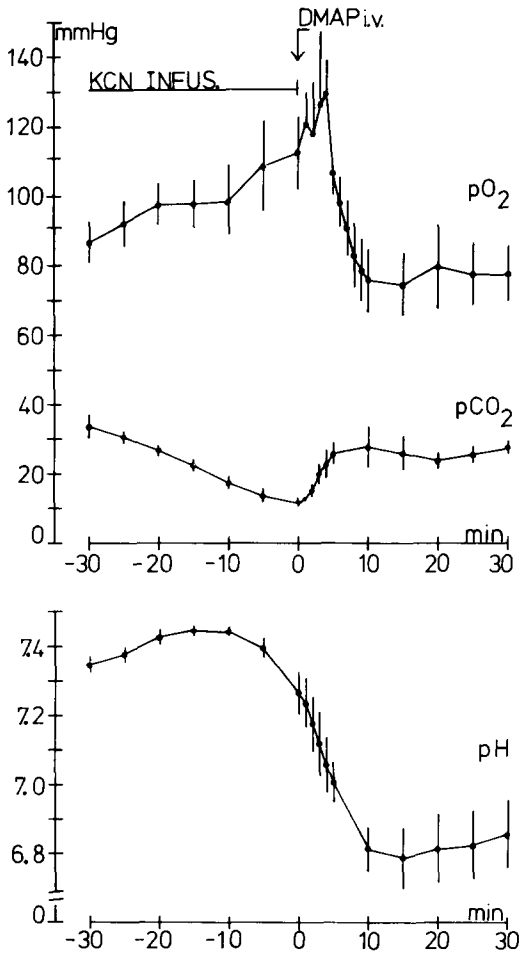

Fig. 2. Arterial pO_2, pCO_2, and pH of chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$ i.v.). Effect of DMAP (3.25 mg/kg i.v.) together with the discontinuation of the infusion 1 min after respiratory arrest. Means ± SE; $n = 3$

Experiments During Artificial Ventilation

The fact that oxygen is released during the oxidation by DMAP of oxygenated ferrohemoglobin and that this entails a transient rise in pO_2 in vivo (Klimmek et al. 1979a, b) has suggested the presumption that oxygen alone, independently of the ferrihemoglobin formed, may produce some of the effects that were measured immediately after injection of DMAP.

Table 1 shows some data reflecting the changes in heat conductivity, brain and oesophagus temperature of artificially ventilated dogs during infusion of KCN, 0.072 mg $kg^{-1} \cdot min^{-1}$. It demonstrates clearly that the breathing of 100% oxygen induced a further increase in heat conductivity and an increase in temperature.

Simultaneously, arterial pCO_2 rose and pH diminished (Table 2). These changes were even more pronounced when the duration of oxygen breathing was

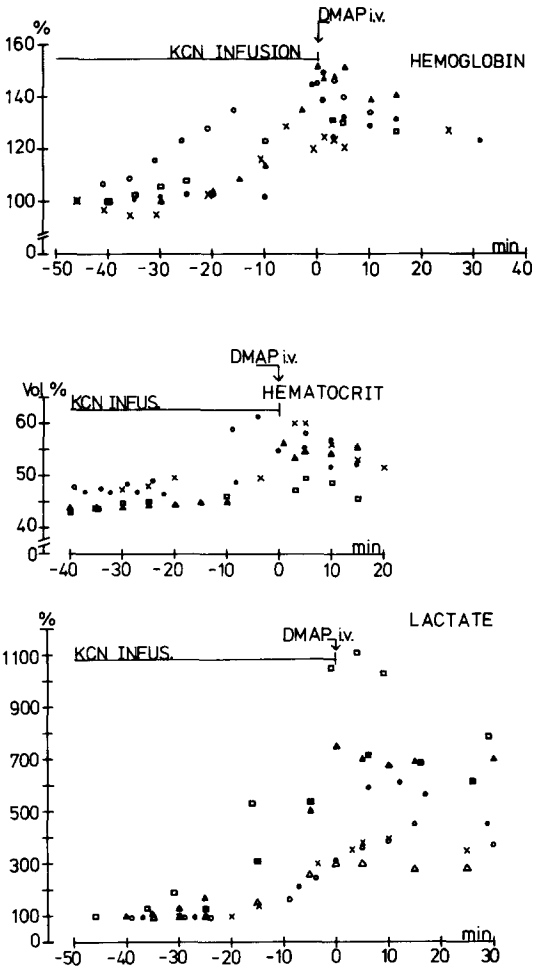

Fig. 3. Total hemoglobin, hematocrit, and lactate concentration in the venous blood of 7 chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$ i.v.). Effect of DMAP (3.25 mg/kg i.v.) together with the discontinuation of the infusion 1 min after respiratory arrest

Table 1. Maximum changes in regional cerebral blood flow and in brain and oesophagus temperature during infusion of KCN, and the influence of 100% oxygen on these changes in chloralose-anesthetized dogs during artificial ventilation. Means ± SE

		Time in which the changes occurred (min)	*n*
KCN infusion (0.072 mg $kg^{-1} \cdot min^{-1}$)			
Heat conductivity (% $\Delta\lambda_{100}$)	+ 31.8 ± 8.0	< 30	5
Brain temperature (°C)	− 0.41 ± 0.07	10	5
Oesophagus temperature (°C)	− 0.4 ± 0.1	10	5
100% oxygen for 3 min while the KCN infusion continued			
Heat conductivity (% $\Delta\lambda_{100}$)	+ 56.9 ± 18.5	3	4
Brain temperature (°C)	+ 0.11 ± 0.04	3	4
Oesophagus temperature (°C)	+ 0.2 ± 0.1	3	5

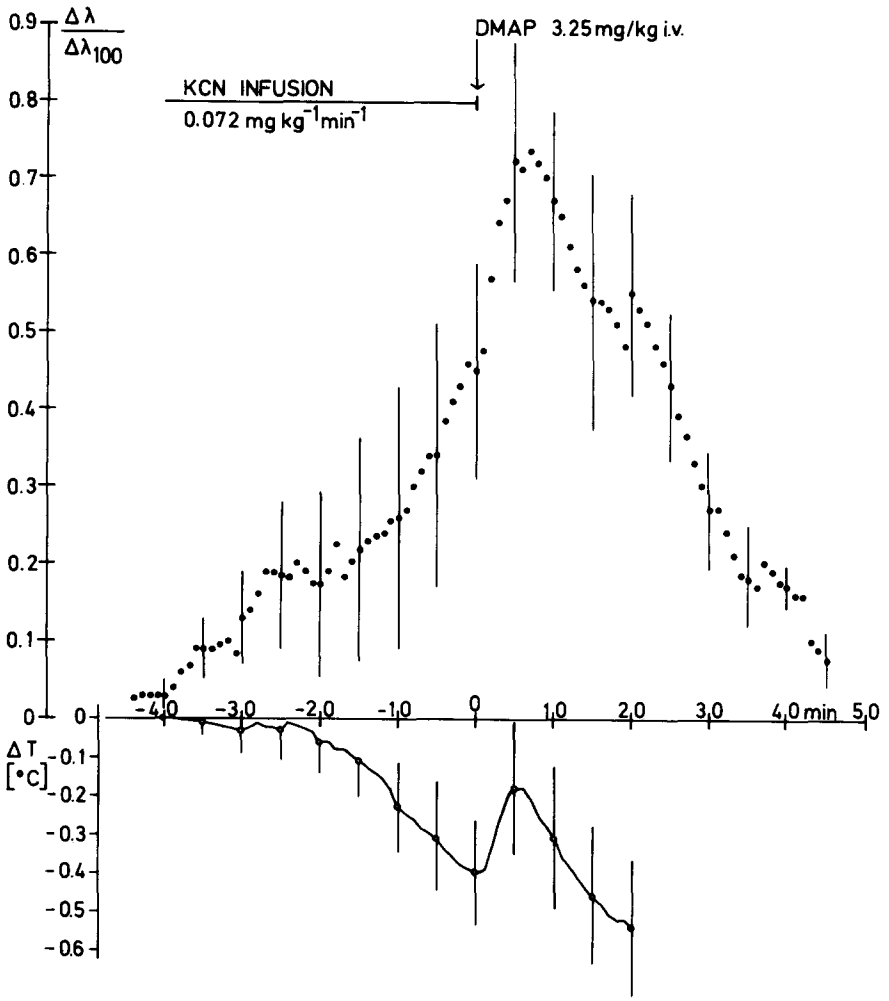

Fig. 4. Changes in brain temperature (ΔT) and in local cerebral blood flow illustrated by the change in heat conductivity $\Delta\lambda/\Delta\lambda_{100}$ in the cingulum of chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$ i.v.). Effect of DMAP (3.25 mg/kg i.v.) together with the discontinuation of the infusion 1 min after respiratory arrest. Means ± SE; $n = 6$

Table 2. Maximal changes in arterial pCO_2 and pH evoked by artificial ventilation with 100% oxygen over 3 or 14 min during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$). For controls 100% oxygen was given before the cyanide infusion began. Means ± SE from four dogs in chloralose anesthesia

Control	During KCN infusion	
	100% oxygen over 3 min	100% oxygen over 14 min
ΔpCO_2 + 1.4 ± 0.5	+ 7.4 ± 1.0	10.0 ± 1.2
ΔpH − 0.02 ± 0.01	− 0.09 ± 0.01	− 0.19 ± 0.04

prolonged from 3 to 14 min and disappeared when the oxygen supply was discontinued.

It is of interest to know how far metabolic inhibition and reactivation or alterations in respiration and circulation are responsible for the changes in blood gases and pH. Therefore, blood gases, pH and blood flow were measured in femoral venous and sinus sagittalis blood of artificially ventilated dogs during infusion of KCN into the femoral or carotid artery.

Figure 5 demonstrates the pattern of pO_2, pCO_2, and pH in the femoral vein during infusion of KCN into the femoral artery, characterized by an increase in pO_2 from 39 ± 7.1 to 84 ± 7.2 mm Hg and a decrease in pCO_2 from 52 ± 3.2 to 37.3 ± 2.6 mm Hg within 20 min; pH did not change. An increase in femoral vein blood flow of 95.6 ± 20.1 ml/min was found after 3 min (Fig. 6).

When cyanide was infused into the carotid artery, a rapid onset of circulatory depression forced a premature discontinuation of the infusion. In the sinus sagittalis, pCO_2 and pH remained stable while pO_2 was rising from 31.7 ± 3.6 to 38.9 ± 2.9 mm Hg within 12 min, and blood flow oscillated slightly without a certain tendency.

Breathing of 100% oxygen for 3 min caused a transient slight rise in pCO_2 in the femoral venous and in the sinus blood, associated with a short-lived

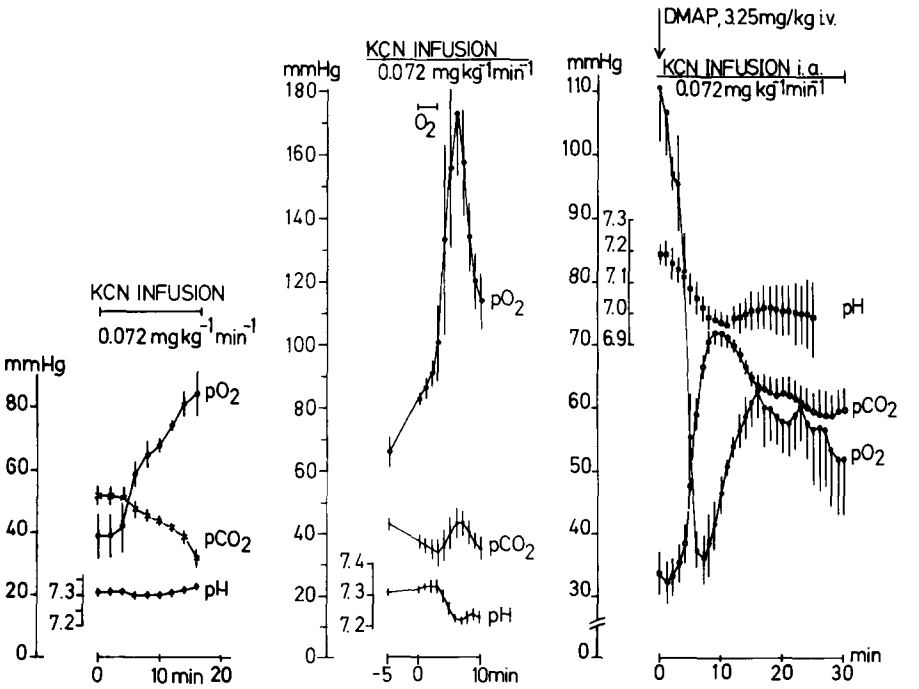

Fig. 5. PO_2, pCO_2, and pH in the femoral venous blood of chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$) into the femoral artery and after breathing of 100% oxygen for 3 min or injection of DMAP (3.25 mg/kg i.v.) without discontinuation of the infusion. Artificial ventilation. Means ± SE; $n = 4$

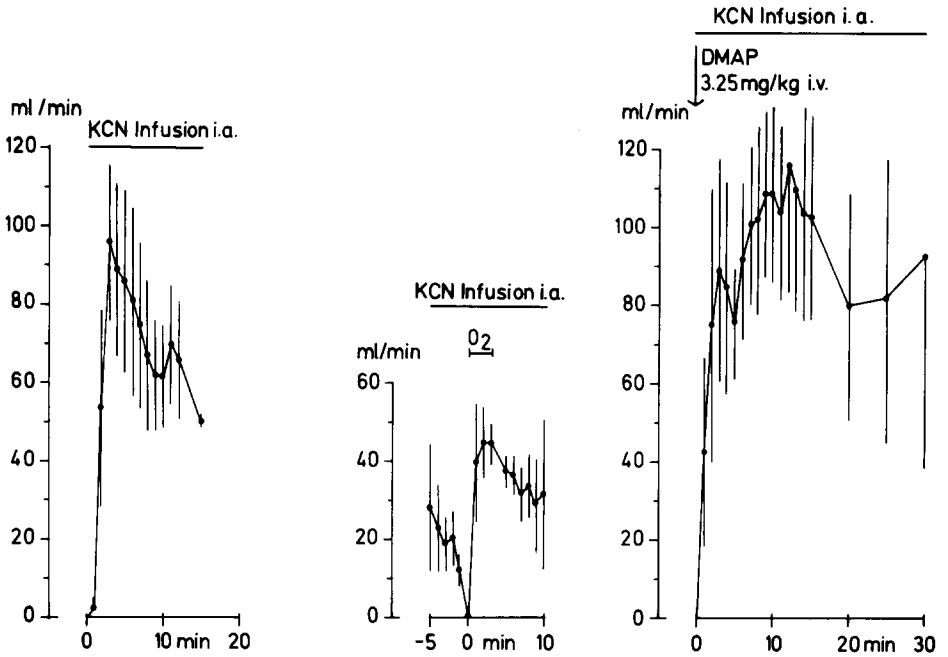

Fig. 6. Changes in the blood flow of the femoral vein of chloralose-anesthetized dogs during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$) into the femoral artery ($n = 4$) and after breathing of 100% oxygen for 3 min ($n = 3$) or injection of DMAP (3.25 mg/kg i.v.; $n = 3$) without discontinuation of the infusion. Artificial ventilation. Means ± SE

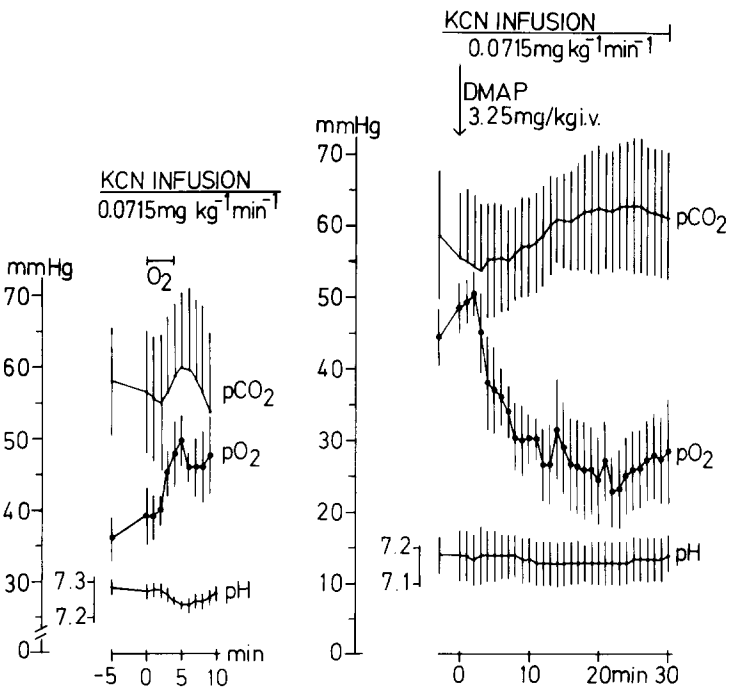

Fig. 7. PO_2, pCO_2, and pH in the sinus sagittalis of chloralose-anesthetized dogs after breathing of 100% oxygen for 3 min ($n = 3$) or injection of DMAP (3.25 mg/kg i.v.; $n = 4$) during infusion of KCN (0.072 mg $kg^{-1} \cdot min^{-1}$) into the carotid artery. Means ± SE

diminution of pH (Fig. 5; Fig. 7) by 0.05–0.1. The oxygen induced a rapid increase in femoral vein blood flow of 45.3 ± 9.3 ml/min within 2 min (Fig. 6) whereas no change was found in the sinus sagittalis.

The influence of DMAP, 3.25 mg/kg i.v., on venous blood gases and pH during infusion of KCN was likewise investigated. In the femoral vein, pO_2 fell from 110.1 ± 8.7 to 36.1 ± 4 mm Hg within 7 min and pCO_2 rose from 33.5 ± 3.6 to 72.3 ± 1.5 mm Hg at 10 min, attended with a diminution of pH from 7.2 to 7; pCO_2 remained elevated and pO_2 rose again (Fig. 5). Femoral blood flow (Fig. 6) increased very quickly by 115.9 ± 32.2 ml/min within 12 min. In the sinus sagittalis, pO_2 decreased from 48.6 ± 3.4 to 24.2 ± 6.2 mm Hg within 20 min with the fastest changes being found in the first 10 min, and pCO_2 increased from 55.7 ± 9.2 to 62.8 ± 8.9 mm Hg within 20 min (Fig. 7). The sinus blood flow showed no definite tendency.

Discussion

In the present experiments, the survival time, i.e., the time until respiratory arrest occurred, was similar to that found by Mercker et al. (1958) when one takes into account the somewhat higher dose of KCN (0.08 mg $kg^{-1} \cdot min^{-1}$) administered by these authors.

The increase in respiratory minute volume and blood pressure and the decrease in heart rate during the infusion of KCN can be accounted for by a reflex mechanism due to the stimulation of chemoreceptors by cyanide. On the other hand, blood pressure is also raised by direct stimulation of the vasomotor center when high doses of KCN, e.g., 10 mg per dog, are injected into the carotid artery (Heymans et al. 1931a, b, 1932). Therefore, a direct and an indirect action of cyanide on the vasomotor center can be postulated. In addition, the higher hematocrit must have contributed to an enhanced peripheral vascular resistance.

The decrease in respiratory minute volume, which always preceded the respiratory arrest, was not associated with an increase in arterial pCO_2, as might be expected from impaired gas exchange in the lungs, but with a continuous decrease in pCO_2 and the onset of a rapid diminution of arterial pH below the initial level. Obviously, the metabolic inhibition and acidosis prevailed at this stage of poisoning.

DMAP restored spontaneous respiration after the slow infusion of cyanide, that had effected an elevated blood pressure when respiratory arrest occurred and DMAP was injected. The circulatory condition presented therefore a better chance of recovery than was found for acute cyanide poisoning, that caused a fall in blood pressure below the critical threshold after a short-lived rise (Klimmek et al. 1979b).

The lack of an increase in the venous pH despite the decrease in pCO_2 of about 20 mm Hg during the infusion of cyanide into the femoral artery of artificially ventilated dogs may result from the accumulation of acid metabolites (Fig. 5); the latter may have contributed to the rapid increase in femoral blood flow. The changes in temperature and blood gases indicate an inhibition of the

aerobic metabolism. This conclusion is given further support by the fact that the intravenous infusion of KCN at a rate of 0.1 mg $kg^{-1} \cdot min^{-1}$ or less reduces the utilization of the inspired oxygen in dogs (Mercker et Roser 1957).

CBF increased during slow intravenous intoxication, that in some way may reflect the situation in case of poisoning by oral ingestion of cyanide. It remains unclear by which mechanism this response is triggered. At the same infusion rate, the administration of cyanide into the carotid artery disturbed the circulatory regulation more rapidly than did the administration into the venous system, thereby requiring a premature discontinuation of the infusion to prevent circulatory failure. Consequently, the metabolic inhibition in the brain was less pronounced than in the femoral region, and a serious depression of the peripheral circulation prevailed due to a high sensitivity of cerebral centers and/or the carotid body to cyanide.

The injection of DMAP was followed by an increase in CBF and blood pressure, whose rise itself may evoke an increase in CBF (Betz 1975). These changes may have been produced by the sudden increase in pCO_2, because an elevated arterial pCO_2 induces high blood pressure by stimulation of chemoreceptors (Heymans et al. 1932) and an increase in CBF by reduction of the resistance in the cerebral arteries, that are especially sensitive to changes in pCO_2 (Reivich 1964).

The question arises how the rise in arterial pCO_2 came about. Mercker and Roser (1957) have demonstrated that the formation of ferrihemoglobin after poisoning by cyanide is followed by a higher utilization of the inspired oxygen. The striking increase in the venous pCO_2 after injection of DMAP may be considered a consequence of enhanced aerobic metabolism whereas the simultaneous rapid fall in the venous pO_2 may have been caused by the ferrihemoglobin formation (Klimmek et al. 1981) and a higher oxygen consumption due to the enhanced aerobic metabolism.

Since there is no evidence in the literature that normobaric or hyperbaric oxygen may displace CN^- from cytochrome oxidase, the elevated venous pCO_2 points to an activation by oxygen of the aerobic tricarboxylic acid cycle in cells that have been insufficiently provided with oxygen, probably by a cyanide-induced impairment of the microcirculation. In this regard it is worth mentioning Grodh and Norberg (1947), who reported a better chance of survival for cyanide-poisoned rabbits due to the breathing of pure oxygen, and the beneficial effects of normobaric oxygen on the EEG (Burrows et al. 1972) and ECG (Cope 1961) of dogs, or the effect of hyperbaric oxygen on the electrical activity of cyanide-poisoned mice (Ivanov 1959). All these findings are supported by the action of pure oxygen on pCO_2, temperature, CBF, and peripheral circulation as demonstrated in our study. The whole body of data justifies the conclusion that breathing of pure oxygen may be of great importance for the improvement of circulation and aerobic metabolism in the brain or other parts of the body after poisoning by cyanide.

The experimental data show that the effect of DMAP in cyanide poisoning may consist in a long-lasting metabolic reactivation by the binding of CN^- to ferrihemoglobin and a short-lasting metabolic activation due to the oxygen released during the oxidation of oxygenated ferrohemoglobin (Klimmek et al.

1979a, b). The elevation of cerebral and peripheral blood flow due to the treatment with DMAP or pure oxygen is likely to accelerate the detoxication of cyanide.

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