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EFFECT ON VENTILATION OF PAPAVERINE ADMINISTERED TO THE BRAIN STEM OF THE ANAESTHETIZED CAT

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SUMMARY

1. To investigate whether cerebral vasodilatation by itself contributes to the decrease in ventilation as found during brain stem hypoxia the role of cerebral vasodilatation on minute ventilation was investigated in twelve cats anaesthetized with α-chloralose–urethane.

2. Cerebral vasodilatation in the medulla oblongata was produced by adding papaverine to the blood perfusing the brain stem.

3. Papaverine at concentrations of 10–35 μg per millilitre of blood had an appreciable depressant effect on ventilation. At a concentration of 14·3 μg ml^{-1} the depression in ventilation averaged $0{\cdot}7 \pm 0{\cdot}1$ l min^{-1}.

4. The ventilatory response to stepwise changes in papaverine concentration could be adequately described with a single exponential function with a time delay.

5. The time constant of the ventilatory response following a step increase in papaverine concentration (134 ± 15 s) was longer than that of the step decrease (105 ± 10 s) in concentration ($P = 0{\cdot}034$). The time delays of the ventilatory response (88 ± 21 s and 53 ± 8 s respectively) were not significantly different ($P = 0{\cdot}126$).

6. The ventilatory response to stimulation of the peripheral chemoreceptors by hypoxia and of the central chemoreceptors by hypercapnia was not impaired by papaverine.

7. The results support the hypothesis that cerebral vasodilatation by itself contributes to the decrease in ventilation by brain stem hypoxia.

INTRODUCTION

It is widely accepted that the chemosensitive structures in the medulla oblongata respond to changes in local tissue P_{CO_2} (P_{t,CO_2}). The value of this P_{t,CO_2} depends among other things on the arterial P_{CO_2} (P_{a,CO_2}), metabolism and blood flow. During acute mild hypoxia the blood flow in the brain stem increases without a change in metabolic rate (Johannson & Siësjo, 1975). This may result in a decrease in P_{t,CO_2} and contribute to the hypoventilation induced by central hypoxia. However, if the blood flow at the site of the central chemoreceptors is high and metabolism is low, as suggested by Severinghaus and co-workers (Severinghaus & Crawford, 1978), the gradient between P_{t,CO_2} and P_{a,CO_2} is expected to be small so that changes in blood

flow would have a small effect on P_{t,CO_2} which consequently could play no significant role in the ventilatory depression by central hypoxia.

Several authors have reported that transient changes in brain blood flow by mechanically produced hypertension with an aortic balloon resulted in a decrease in ventilation (Neubauer, Santiago, Posner & Edelman, 1985; Green, Darnall, Bierd & Adams, 1989). However, with this technique transient effects only could be studied.

It is the aim of this study to assess the effect of vasodilatation of medullary blood vessels on ventilation. To achieve this we used papaverine which has been shown to increase cerebral blood flow in the medulla oblongata (Conway & Weiss, 1980). We infused papaverine into the vertebral artery of cats using the technique of artificial brain stem perfusion.

METHODS

In twelve adult cats of either sex weighing 2·4–4·3 kg anaesthesia was induced with 15 mg kg^{-1} ketamine (I.M.) and atropine (0·5 mg S.C.). This was followed by inhalation of a gas mixture containing 0·5–1·5 % halothane and 30 % O_2 in N_2. After cannulation of the right femoral vein, 20 mg kg^{-1} α-chloralose and 100 mg kg^{-1} urethane were slowly injected. Simultaneously the halothane concentration in the inspirate was reduced to zero. Anaesthesia was then maintained with a continuous infusion of 1 mg kg^{-1} h^{-1} α-chloralose and 5 mg kg^{-1} h^{-1} urethane. Rectal temperature was monitored with a thermistor and maintained within 0·5 °C in the range from 36·3–39·0 °C by a heating pad and an infra-red lamp.

The trachea was cannulated through a tracheostomy and connected via a flow transducer (Fleisch no. 0, Switzerland) to a T-piece. One arm of the T-piece received a flow of gas from a gas mixing system in excess of the inspiratory demand. By adjusting the composition of the inspiratory gas the end-tidal CO_2 and O_2 could be set at any desired level.

The left femoral artery and vein were cannulated and an extra corporeal circuit (ECC) was fitted between the two cannulas. In the neck region a branch of the vertebral artery was dissected free from surrounding tissue and cannulated; the contralateral vertebral artery was clamped. Subsequently blood from the femoral artery was pumped via the ECC into the cannulated vertebral artery at a flow rate of 7–8 ml min^{-1}. The P_{a,CO_2} and P_{a,O_2} of this blood (called P_{a^c,CO_2} and P_{a^c,O_2}) was adjusted by means of a gas exchanger which formed part of the ECC. These blood gas tensions were manipulated independently of those in the systemic circulation (called P_{a^p,CO_2} and P_{a^p,O_2}). Details about the surgical procedures and the ECC have been previously described (Berkenbosch, Heeringa, Olievier & Kruyt, 1979; Berkenbosch, Ward, Olievier, DeGoede & Van Hartevelt, 1989*b*).

Measurements

Inspiratory and expiratory flow were measured using the Fleisch pneumotachograph connected to a differential pressure transducer (Statham, USA). The flow signal was electronically integrated to yield a volume signal. The CO_2 concentration in the tracheal gas was measured with a fast infra-red analyser (Gould Godart Mk2 capnograph, the Netherlands) and the O_2 tension with a fast zirconium oxide cell (Jaeger O_2 test, Germany). Blood gas tensions in the two circulatory systems were measured continuously with P_{CO_2} electrodes (General Electric type A 3128AB, USA) and with Clark-type home-made O_2 electrodes (outer diameter 1 mm) placed in cuvettes in the ECC. The O_2 and CO_2 electrodes were calibrated with water equilibrated with CO_2–O_2–N_2 gas mixtures delivered by a gas mixing pump (Wösthoff type M300-AF, Germany). Every 2–3 h the acid–base status of the animals was determined with a conventional sample method (Radiometer BMS 2 MK2, Denmark) in blood samples drawn from the femoral artery. Femoral artery blood pressure and perfusion pressure were measured using Statham pressure transducers. All signals were recorded on polygraphs, digitized (sample frequency 40 Hz) and processed by a PDP 11/23 minicomputer (Digital Equipment Corp., Ireland) and stored on disc. Steady-state values of ventilation, central and peripheral arterial blood gas tensions and blood pressure were averaged over twenty breaths. Details about the measurement techniques have been previously described (Berkenbosch *et al.* 1979).

Experimental designs

In all cats experiments were performed with the brain stem perfused with hyperoxic blood (mean P_{a^c,O_2} 50·6 kPa (380 mmHg)). The P_{a^c,CO_2} was set at a slightly hypercapnic level (mean 5·6 kPa (42 mmHg); range 4·8–7·3 kPa (36–55 mmHg)) so that a constant CO_2 tension in the systemic circulation could be maintained even at the lowest level of ventilation. The P_{CO_2} in the systemic circulation was kept constant by adding CO_2 to the inspired gas which consisted of 60 % O_2 in N_2. Among cats this P_{a^p,CO_2} varied from 5·2 to 7·5 kPa (mean 6·0 kPa) (39–56 mmHg (mean 45 mmHg)). The mean P_{a^p,O_2} was 47·3 kPa (355 mmHg). The acid–base status of the animals was in the normal range for cats (mean base excess $-8{\cdot}2 \pm 2{\cdot}4$; range from $-4{\cdot}3$ to $-12{\cdot}5$ mmol l^{-1}) and as it remained constant, within 2 mmol l^{-1}, during the measurements we did not need to correct it by infusion of bicarbonate.

In eight cats the effect of papaverine on ventilation was assessed. To do this a solution containing 1 mg papaverine per millilitre of saline was infused into the blood by which the brain stem was artificially perfused. Steady-state ventilation was measured at three different papaverine concentrations in the range of 5–35 μg per millilitre of blood. The time course of the ventilation to suddenly starting or cessation of the papaverine infusion was assessed on a breath-by-breath basis. In each cat one to two such responses were measured using a papaverine concentration in the blood of 14·3 μg ml^{-1}.

In eleven cats the ventilatory response to stimulation of the peripheral chemoreceptors by isocapnic hypoxia was assessed during perfusion of the brain stem with blood with and without papaverine (14·3 μg ml^{-1}). By manipulating the inspired O_2 and CO_2 concentration the P_{a^p,O_2} was lowered from a hyperoxic value of 47·3 kPa (355 mmHg) to a moderate hypoxic value of 6·3 kPa (47 mmHg) (range 5·1–8·0 kPa (38–60 mmHg)) while the P_{a^p,CO_2} was kept constant. Steady-state ventilation was measured 1 min before and during the last minute of the hypoxic challenge which lasted 5 min. In each cat one to three such responses were measured.

In five cats the effect on steady-state ventilation of a change in P_{a^c,CO_2} was measured with and without papaverine. To do this the P_{a^c,CO_2} was increased by 0·9 kPa (6·8 mmHg) (range 0·5–1·2 kPa (3·7–9·0 mmHg)) while the other blood gas tensions were kept constant. Ventilation was measured before and about 10–15 min after the change in P_{a^c,CO_2} when a near steady state was reached. These measurements were repeated during perfusion of blood with a papaverine concentration of 14·3 μg ml^{-1}. The total amount of papaverine infused varied among cats between 6 and 16 mg.

Data analysis

The time course of the breath-by-breath ventilation ($\dot{V}_E$) following a step change in papaverine concentration was analysed by fitting a single-exponential function with a time delay to the data using the following model:

$$\dot{V}_E = \dot{V}_0 + \Delta\dot{V}\{1 - \exp[(t - T_d)/\tau]\}; t > T_d,$$

where $\dot{V}_E = \dot{V}_0$ (the initial ventilation for $t < T_d$), $\Delta\dot{V}$ is the increment or decrement in ventilation, τ is the time constant and T_d is a time delay. Time 0 is the time of the start of papaverine infusion. The transit time of the blood from the place where the papaverine was infused to the vertebral artery was about 15 s. The ventilatory on- and off-responses were fitted separately by means of a least-squares estimation technique.

Statistical analysis

Mean values of parameters of each cat without (control) and during papaverine administration were calculated and Student's paired t test was used to detect differences between parameters taking a P value of 0·05 as level of significance.

RESULTS

Time course of ventilatory response

Figure 1 shows a recording of an experiment in which a step decrease in papaverine concentration of the blood perfusing the brain stem was made from 14·3 to 0 μg ml^{-1}. After about half a minute ventilation started to increase mainly through a change in

tidal volume. The end-tidal CO_2 and O_2 concentrations were kept constant so that the blood gas tensions at the level of the peripheral chemoreceptors did not change during this manoeuvre. Soon after the cessation of the papaverine infusion a small but distinct increase of the pressure in the cannula located in the vertebral artery was seen. The effect on systemic arterial pressure was negligible.

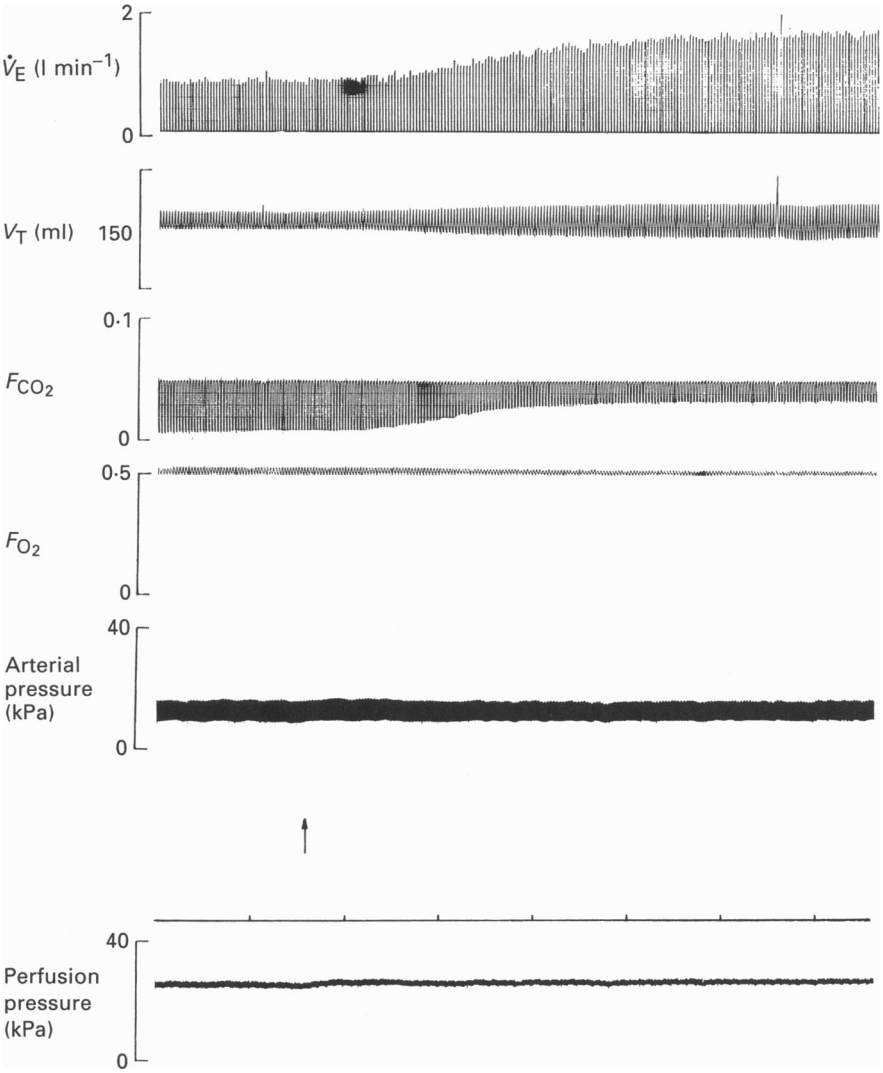

Fig. 1. Example of original recordings of tidal volume (V_T), breath-by-breath ventilation ($\dot{V}_E$) and blood pressure after cessation of infusion of papaverine (arrow) in the blood perfusing the brain stem. F_{CO_2} and F_{O_2} denote fractions of CO_2 and O_2 in tracheal gas. Also shown is the pressure measured in the cannula connected to the vertebral artery (perfusion pressure). Note that soon after cessation of papaverine infusion the perfusion pressure increased. The distance between the tickmarks on the line above the tracing of the perfusion pressure indicates 1 min intervals.

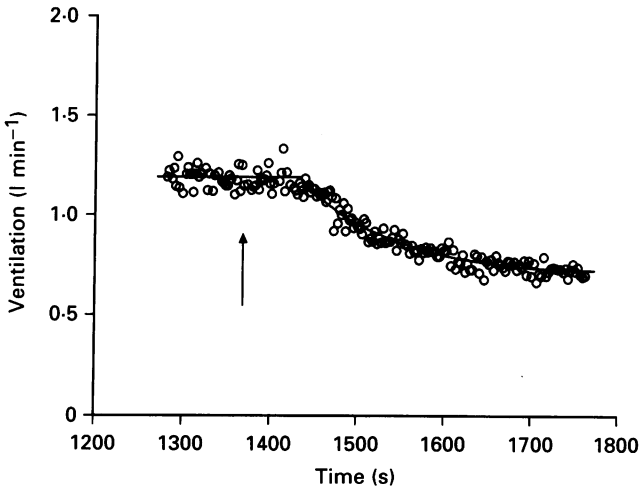

Fig. 2. Breath-by-breath ventilatory response to a step increase in papaverine concentration from 0 to 14·3 μg ml^{-1} in the blood perfusing the brain stem. At the arrow the infusion of papaverine was started. Continuous line, model fit to this data set. Estimated parameters: $\dot{V}_0$, 1·2 l min^{-1}; $\Delta\dot{V}$, −0·51 l min^{-1}; τ, 114·4 s; T_d, 58 s.

TABLE 1. Time constants, time delays and ventilatory changes for step increase and decrease in papaverine concentration

Expt	τ_{on} (s)	$\Delta\dot{V}$ (l min^{-1})	$T_{d,on}$ (s)	Runs	τ_{off} (s)	$\Delta\dot{V}$ (l min^{-1})	$T_{d,off}$ (s)	Runs
801	106·7	0·47	37·8	1	104·9	−0·79	63·5	2
802	97·1	0·53	84·3	3	183·3	−0·68	159·8	1
807	90·7	0·78	95·0	1	108·6	−1·15	49·9	2
818	161·4	0·58	85·8	2	204·4	−0·44	51·8	1
906	128·1	0·76	51·1	3	153·5	−0·93	70·1	2
908	95·4	0·29	46·8	2	83·6	−0·25	137·2	1
919	76·0	0·89	95·6	2	129·9	−0·83	211·4	1
921	84·5	0·60	50·1	1	105·6	−0·52	82·1	1
Mean	105·0	0·61	68·3		134·2	−0·70	103·2	
S.E.M.	9·8	0·07	8·5		15·0	0·10	21·0	

Values are means. τ, time constant; T_d, time delay; $\Delta\dot{V}$, ventilatory change. 'On' refers to ventilatory on-response and 'off' to ventilatory off-response.

A total of eleven step increases and fifteen step decreases in papaverine concentration were analysed. Figure 2 illustrates the breath-by-breath data for a step increase in papaverine concentration from 0 to 14·3 μg ml^{-1} together with the model fit to this data set. After a time delay of about 1 min ventilation started to decrease in an exponential fashion and a new steady state was reached after 6 min. The estimated parameters of all runs are summarized in Table 1. Since we made three comparisons we take as level of significance $P \leqslant 0{\cdot}017$ (Bonferroni correction). The time constant of the ventilatory on-response was shorter than that of the off-response but did not quite reach the level of significance ($P = 0{\cdot}034$). The respective time delays ($P = 0{\cdot}126$) and changes in ventilation ($P = 0{\cdot}248$) were not significantly different.

Dose–effect relation

The effect of different concentrations of papaverine on ventilation and blood pressure was evaluated by measuring the change in ventilation and blood pressure taking as reference value the ventilation during perfusion of the brain stem with

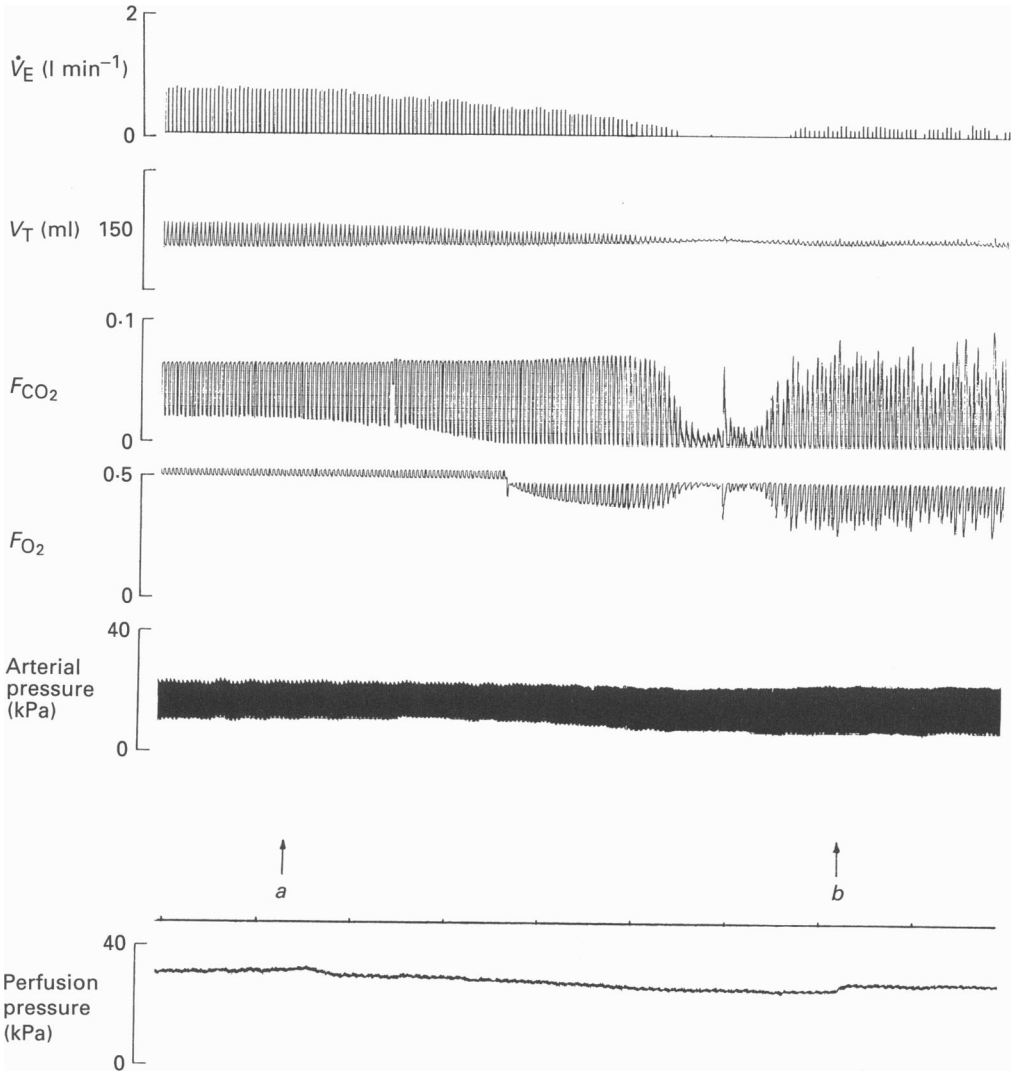

Fig. 3. Recording of an experiment in which infusion of papaverine (arrow at *a*) with a concentration of 35 μg ml^{-1} resulted in apnoea. The $P_{a^c.CO_2}$ was 4·8 kPa (36 mmHg), the $P_{a^p.CO_2}$ 6·8 kPa (51 mmHg) and the $P_{a^p.O_2}$ about 48 kPa (360 mmHg). The animal started to breathe again due to stimulation of the peripheral chemoreceptors by the changed blood gas tensions in the systemic circulation ($P_{a^p.CO_2}$ 12 kPa (90 mmHg), $P_{a^p.O_2}$ 15 kPa (113 mmHg)) but tidal volume was too small to give reliable measurements of end-tidal gas tensions. At arrow *b* the perfusion flow rate was increased from 7 to 8 ml min^{-1}. The distance between the tickmarks on the line above the tracing of the perfusion pressure indicates 1 min intervals.

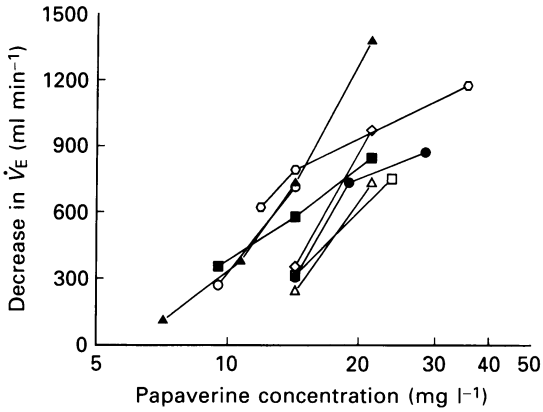

Fig. 4. Semilogarithmic plot of the decrease in ventilation against the papaverine concentration in the blood perfusing the brain stem.

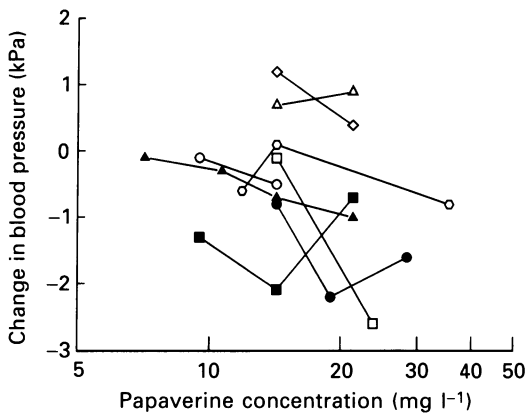

Fig. 5. Semilogarithmic plot of the change in blood pressure against the papaverine concentration.

blood free from papaverine. The results are shown in Figs 4 and 5. The higher the papaverine concentration the stronger the depression of ventilation. Papaverine concentrations higher than 35 μg ml^{-1} resulted in apnoea when the P_{a^c,CO_2} was lower than 4·8 kPa (36 mmHg) (Fig. 3). As a result the blood gas tensions in the systemic circulation changed to such values that the animal started to breathe again due to stimulation of the peripheral chemoreceptors. At P_{a^c,CO_2} values above 5·8 kPa (43·5 mmHg) we did not observe apnoea but due to the large ventilatory depression at papaverine concentrations above 35 μg ml^{-1} it was difficult to keep the blood gas tensions in the systemic circulation constant and within reasonable limits. Papaverine concentrations higher than 35 μg ml^{-1} were therefore not investigated. In most experiments we used a papaverine concentration of 14·3 μg ml^{-1}. The ventilatory depression at this concentration is about equal to a central hypoxic depression of about 0·6 l min^{-1} at a P_{a^c,O_2} of 6·5 kPa (49 mmHg) (VanBeek, Berkenbosch, DeGoede & Olievier, 1984). Figure 5 shows that there was no

consistent tendency in the change in systemic blood pressure. The systemic blood pressure (mean 15·0 kPa (113 mmHg), range 11·7–19·2 kPa (88–144 mmHg)) decreased at a concentration of 14·3 μg ml^{-1} with 0·3 $\pm$ 0·3 kPa (2·3 $\pm$ 2·3 mmHg) (mean $\pm$ S.E.M.).

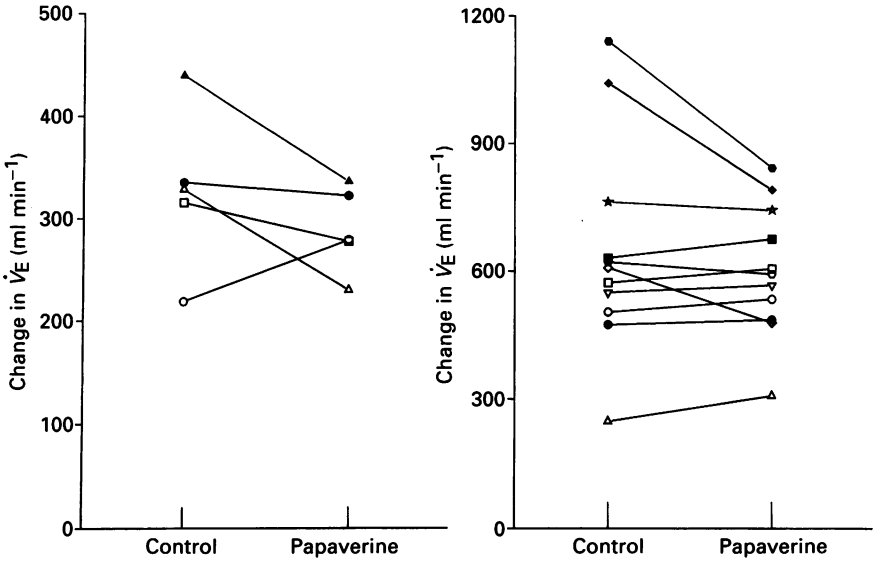

Fig. 6. Ventilatory responses to stimulation of central chemoreceptors (left panel; central CO_2 effect) and peripheral chemoreceptors (right panel; peripheral O_2 effect) during perfusion of the brain stem with blood, without (control) and with papaverine at a concentration of 14·3 μg ml^{-1}.

Peripheral O_2 and central CO_2 effects

Stimulation of the peripheral chemoreceptors by lowering the P_{a^p,O_2} isocapnically from hyperoxia to 6·3 kPa (47 mmHg) resulted in an increase in ventilation of 650 $\pm$ 76 ml min^{-1} (mean $\pm$ S.E.M.). During infusion of papaverine into the blood perfusing the brain stem the same change in P_{a^p,O_2} caused an increase in ventilation of 603 $\pm$ 47 ml min^{-1} which was not significantly different from the change in ventilation without infusion of papaverine ($P = 0·224$). When the central chemoreceptors were stimulated by increasing the P_{CO_2} of the blood perfusing the brain stem, keeping the other blood gas tensions constant, the increase in ventilation (328 $\pm$ 35 ml min^{-1}) was not significantly different from the value (290 $\pm$ 19 ml min^{-1}) obtained by applying the same change in P_{a^c,CO_2} during infusion of papaverine ($P = 0·279$). The results are illustrated in Fig. 6 and indicate that the ventilatory response to stimulation of the peripheral chemoreceptors by hypoxia and of the central chemoreceptors by hypercapnia are not impaired by papaverine applied to the brain stem.

DISCUSSION

With the use of the technique of artificial perfusion of the brain stem we administered papaverine to the blood perfusing the medulla oblongata and pons. The vertebral arteries are in open connection with the circle of Willis via the basilar

artery and the surplus of the infused blood not drawn by the medullary tissues can reach the cerebellum. Since the blood from the ponto-medullary region drains off into the systemic circulation papaverine reached other parts of the body too but at a much lower concentration than in the blood perfusing the brain stem. The dose we used calculated per kilogram body weight was about $30\ \mu g\ kg^{-1}\ min^{-1}$, substantially less than in other studies. It is therefore not surprising that we did not observe a significant decrease in blood pressure as was found by others (Conway & Weiss, 1980; Date & Hossmann, 1984). Nikolov & Leniger-Follert (1978) reported that only intracarotid infusion of more than $500\ \mu g\ kg^{-1}\ min^{-1}$ resulted in a slight decrease in blood pressure.

We frequently observed a small decrease in the 'perfusion pressure' when papaverine was infused and an increase after cessation. The pressure measured upstream from the tip of the cannula located in a branch of the vertebral artery is called perfusion pressure. The diameter of this branch is very small (about 0·4 mm) and the length which could be exposed was usually less than 4 mm. This causes an unfavourable position of the tip of the cannula in the blood vessel resulting in a high flow resistance and therefore the pressure in the upstream segment was appreciably higher than the systemic blood pressure. The difference between the measured perfusion pressure and systemic blood pressure not only depends on the flow resistance of the cannula but also on the resistance of the vascular bed downstream of the cannula. The systemic blood pressure remained constant immediately after the start of the papaverine infusion so that the observed small change in perfusion pressure indicates a change in vascular resistance of the medulla and pons (see Figs 1 and 3).

The chief pharmacological action of papaverine is the relaxation of smooth muscle. Papaverine is not related chemically or pharmacologically to the opioid alkaloids and it has no narcotic effects (Sokoloff, 1959; Needleman, Corr & Johnson, 1985). Our study shows that centrally administered papaverine has a considerable depressant effect on ventilation while the ventilatory responses due to stimulation of the peripheral and central chemoreceptors are completely preserved. It is therefore unlikely that respiratory neurons in the brain stem are impaired by papaverine although such an effect cannot entirely be ruled out. It is more probable that the depression of the ventilation is due to a decreased P_{t,CO_2} as a result of an increase in cerebral blood flow. Papaverine has been shown to increase cerebral blood flow in all regions of the brain with the pons and medulla oblongata as the most responsive parts of the brain (Conway & Weiss, 1980). These effects of papaverine were still observed when hypoxia or hypercapnia were induced (Haggendal, 1965; Wilson, Traystman & Rapela, 1985). Furthermore it has been shown in cats that not only cerebral blood flow increases but also cortical brain tissue P_{O_2} is enhanced and tissue P_{CO_2} decreased (Saratikov & Dmitrienko, 1975; Nikolov & Leniger-Follert, 1978; Pinard & Seylaz, 1978). However, we could not find information about the effect of papaverine on the P_{t,CO_2} of the medulla oblongata.

Based on measurements of the time course of the ventilation to stepwise changes in end-tidal P_{CO_2} it was suggested that the central chemosensitive structures are relatively overperfused (Severinghaus & Crawford, 1978) and therefore the P_{t,CO_2}–P_{a,CO_2} gradient is small. Local vasodilatation then would have a minor effect on the P_{t,CO_2} at the site of the central chemoreceptors and consequently on

ventilation. Unfortunately, there is no agreement on the magnitude of the P_{t,CO_2}–P_{a,CO_2} gradient in the medulla oblongata. As an approximation of the P_{t,CO_2}, the ECF P_{CO_2} at the ventral side of the medulla oblongata, where presumably the central chemoreceptors are located, is taken. Javaheri & Teppema (1987) measured an ECF P_{CO_2} about 2 kPa (15 mmHg) higher than arterial P_{CO_2}, Feustel, Vurek &

TABLE 2. Time constants and time delays for ventilatory responses to stepwise changes in CO_2, O_2 and papaverine in blood perfusing the medulla oblongata

	Ventilatory on-response		Ventilatory off-response	
	τ_{on} (s)	$T_{d,on}$ (s)	τ_{off} (s)	$T_{d,off}$ (s)
Hypercapnia*	87±10	5±3	150±19	−1±3
Hypoxia†	106±10	18±4	150±9	25±4
Papaverine	105±10	53±8	134±15	88±21

Values are means±S.E.M. τ, time constant; T_d, time delay which is adjusted for the transport time of the CO_2, O_2 and papaverine disturbance in the tubing to the vertebral artery.

* Data from Berkenbosch *et al.* (1989*b*).

† Data from Ward *et al.* (1990).

Severinghaus (1983) reported gradients of about 1·3 kPa (10 mmHg) while Stafford, Feustel & Severinghaus (1983) found a difference of 0·5 kPa (3·8 mmHg). Our study shows that cerebral vasodilatation has an appreciable effect on ventilation. Therefore it is not very probable that the central chemoreceptors are overperfused. There is some additional evidence, although indirect, that an increase in cerebral blood flow has an appreciable effect on ventilation. For instance we recently found a difference of about 85% between the ventilatory CO_2 sensitivity measured with Read's rebreathing method and the steady-state method (Berkenbosch, Bovill, Dahan, DeGoede & Olievier, 1989*a*). This difference could be fully explained by the effects of CO_2 on cerebral blood flow at the site of the central chemoreceptors.

In Table 2 the time constants and time delays found in this study for the ventilatory increase and decrease due to papaverine are compared with those found in earlier studies of our group for the ventilatory response to stepwise changes in P_{O_2} and P_{CO_2} of the blood perfusing the brain stem (Berkenbosch *et al.* 1989*b*; Ward, Berkenbosch, DeGoede & Olievier, 1990). The agreement in time constants is striking. This suggests a common mechanism as cause for these responses, namely the unloading or loading with CO_2 of the brain tissue at the site of the central chemoreceptors, which for hypoxia and papaverine then would be due to a change in cerebral blood flow. The time delays for the papaverine effect were longer than for hypoxia. However, as argued earlier, the dynamics of the change in cerebral blood flow are mainly reflected in an apparent time delay that compares favourably with the one experimentally found for the hypoxic steps (DeGoede & Olofsen, 1989). Information about the dynamics of the effect of papaverine on cerebral blood flow is not present, but it is quite possible that the response of the cerebral blood flow to papaverine is somewhat slower than that for hypoxia resulting in a larger apparent time delay. In the anaesthetized cat the increase in cerebral blood flow during

hypoxia should therefore be taken into consideration as a cause for the central depressant effect of hypoxia on ventilation especially at moderate levels of hypoxia when impairment of respiratory neurons due to metabolic failure or the synthesis of neuromodulators inhibiting ventilation is unlikely.

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