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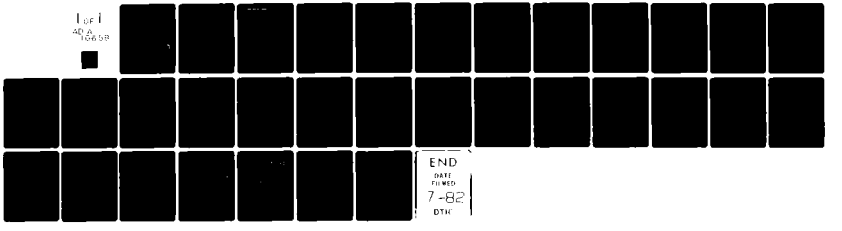

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We studied the effect of ablating the carotid bodies (CBx) on resting pulmonary ventilation of awake goats, on composition of their arterial blood and CSF, and on responses to respiratory stimuli (hypercapnia, hypoxia, injection of cyanide). Hyperventilation in response to acute hypoxia was abolished. The ventilatory response to injection of cyanide was markedly diminished but not completely abolished after CVx; onset of the response was delayed and the interaction of cyanide and hypoxia appeared eliminated. Resting pulomonary ventil-

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VENTILATORY RESPONSIVENESS OF GOATS WITH ABLATED CAROTID BODIES.

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ABSTRACT

We studied the effect of ablating the carotid bodies (CBx) on resting pulmonary ventilation of awake goats, on composition of their arterial blood and CSF, and on responses to respiratory stimuli (hypercapnia, hypoxia, injection of cyanide). Hyperventilation in response to acute hypoxia was abolished. The ventilatory response to injection of cyanide was markedly diminished but not completely abolished after CBx; onset of the response was delayed and the interaction of cyanide and hypoxia appeared eliminated. Resting pulmonary ventilation was reduced by almost one fifth, and $PaCO_2$ was increased following CBx. In CSF, pH and PCO_2 were not different before and after CBx, suggesting that the stimulus for the central chemoreceptor was not diminished. The difference in PCO_2 between arterial blood and CSF was reduced after CBx. In spite of the resting hypercapnia after CBx, the goats responded to hyperoxic CO_2 rebreathing with a similar increase in ventilation before and after CBx. We conclude that the carotid bodies contribute significantly to the resting respiratory drive in normoxic goats. The increase in ventilation in response to acute hypercapnia appears to be mediated by the central chemoreceptors.

Key words: CO_2 production, CSF, CO_2 rebreathing, cyanide, awake goats

INTRODUCTION

Controversies still exist concerning contribution of the peripheral chemoreceptors to the total ventilatory drive. There is general agreement that after ablation of the carotid bodies (CBx) the ventilatory response to hypoxia is abolished. Quantitative contribution of the carotid bodies (CB) to resting ventilatory drive is uncertain: most studies conclude that CBx leads to decrease in resting pulmonary ventilation with hypercapnia (3, 4, 11, 30), while some disagree (18). Both decreased and undiminished responsiveness to CO_2 after CBx have been reported (16, 18, 27, 30). We report the results of a study in unanesthetized goats, designed to evaluate the effect of CBx on resting ventilation, on composition of arterial blood and CSF (the latter as an indicator of input into the "central" chemoreceptors), and on ventilatory responsiveness to chemical stimuli (hypercapnia, hypoxia, hyperoxia). We also present observations on the effect of CBx on the ventilatory response to injection of cyanide, a time-honored test for detecting the functional integrity of the peripheral chemoreceptors (21).

METHODS

Operative Procedures

Skin-denervated carotid loops were produced in goats for sampling arterial blood, and nylon guide tubes were implanted in the occipital bones for repeated sampling of CSF, following the techniques of Pappenheimer et al (22).

The carotid bodies were excised under general anesthesia. From a ventral midline incision in the neck, the carotid arteries and their bifurcations were exposed by blunt dissection between the sternocephalic and sternohyoid muscles. The adventitia was dissected from the arterial walls, from 3-4 cm below to an equal distance above the bifurcation, and all visible nerve fibers close to the bifurcation were resected. Saturated solution of phenol in 95% ethyl alcohol was applied to the denuded arterial walls with a sterile cotton-tipped applicator, which produced necrosis of the superficial layer. The area was then flushed with sterile saline, and the wound sutured in layers. The wounds healed within two weeks. The effect of this intervention was tested during the 3rd or 5th week after operation and again five months later by injecting a bolus of cyanide into the pulmonary artery, as described below.

Experimental Design

We studied five goats weighing 36-48 kg (mean 42 kg). Each goat was studied twice before and twice after CBx. Means of the two measurements in each condition were used for data analysis.

On each experimental day, we punctured the cisterna magna through the guide tube, without anesthesia, and percutaneously inserted a plastic catheter into the carotid artery in the denervated skin loop. We then measured resting ventilation ($\dot{V}_E$) and CO_2 production ($\dot{V}_{CO_2}$) and anaerobically withdrew a sample of cisternal CSF. Finally, we tested ventilatory responsiveness to CO_2 using a modification of Read's method of hyperoxic rebreathing (25).

Blood pressure in the carotid and pulmonary artery was measured with transducers (Statham 23DB and 23DC).

Respiratory Measurements

A latex rubber respiratory mask was fitted over the goat's snout. Volume of expired gas was measured with a Wedge spirometer (Med-Science Electronics), while concentration of CO_2 and O_2 at the airway was measured with an infrared analyzer (Beckman LB-2) and a mass spectrometer (Perkin Elmer). Outputs of the gas analyzers and Wedge spirometer were displayed on a Brush strip-chart recorder (Gould Inc.) and recorded with a magnetic tape recorder (Hewlett Packard, Model 3968). Ventilation was calculated breath-by-breath by computer.

For measurement of $\dot{V}_E$ and $\dot{V}CO_2$, the goats inhaled room air through a low resistance valve (J-valve, dead space 92 ml; Warren E. Collins). Arterial blood was sampled and expired minute ventilation and PCO_2 in mixed expired gas measured when a steady state in gas exchange was apparent from stability of the end-tidal PCO_2 ($PETCO_2$). Alveolar ventilation ($\dot{V}_A$) was calculated using Enghoff's modification of Bohr's formula for respiratory dead space. The ventilatory data were normalized to body weight 40 kg.

During CO_2 rebreathing, the respiratory mask was connected through short-length wide-bore tubing to a three-way Y valve. One of the ports of the valve was open to air, the other connected to a rebreathing bag enclosed in a rigid box. The box was connected by wide-bore tubing to a Wedge spirometer. Gas continuously sampled at the junction of the mask and tubing was analyzed for CO_2. Each

rebreathing test was begun with 5 liters of gas (7% CO_2, balance O_2) in the bag. When end-tidal PCO_2 was stable with the goat inhaling room air, the Y valve was turned at end-expiration so that the goat would subsequently inspire from and expire into the rebreathing bag. Rebreathing continued until $P_{ET}CO_2$ was about 65 torr, or until the goat became restless (Figure 1, top). Three to five runs of rebreathing were performed on each experimental day, separated by 10 minute periods of breathing room air. Minute ventilation was plotted breath-by-breath as a function of the simultaneously measured $P_{ET}CO_2$, and linear regressions were calculated for these plots. Ventilatory responsiveness to CO_2 was evaluated from slopes of these plots and from values of $\dot{V}_E$ at $P_{ET}CO_2$ = 60 torr (Figure 1, bottom).

Figure 1

Testing the Effect of Ablation of Carotid Bodies

A balloon-tipped catheter was introduced percutaneously into the pulmonary artery from the external jugular vein. The goats breathed through a mask and a non-rebreathing valve into a circuit made up of wide-bore tubing and a CO_2 absorber, with a T-piece connector leading to a bag-in-box. Pulmonary ventilation was measured with a Wedge spirometer attached to the box. Flow of oxygen and nitrogen into the circuit was controlled with flowmeters to produce hyperoxia or hypoxia. PCO_2 and PO_2 were monitored continuously at the airway. When end-tidal PCO_2, PO_2 and ventilation were stable, a bolus of cyanide (1 μM/kg body weight, as sodium or potassium salt, in 3 ml of saline) was injected into the pulmonary artery. Injections of blanks (3 ml saline or 1 μM/kg KCl in 3 ml saline) did not elicit

any ventilatory response. The response to cyanide injection was quantitated by computer as liters of ventilation in excess of the control value, integrated over time of the duration of response (Δ V, liters, BTPS).

Analytical Techniques

PCO_2, PO_2 and pH in arterial blood and CSF were measured at 37C with Radiometer electrodes and electronics (BMS 3 MK2); corrections were made for rectal temperature (13, 20). The electrodes were calibrated with precision buffers (Radiometer) and with gases analyzed for O_2 and CO_2 with the Scholander apparatus. CO_2 concentration (CCO_2) in CSF was measured with a Natelson microgasometer (Scientific Industries). [Cl^-] was measured in anaerobically separated plasma and in CSF by potentiometric titration (Aminco-Cotlove, American Instruments). [HCO_3^-] in plasma and in CSF were calculated from measured pH and PCO_2 or CCO_2 using published values for pK' and CO_2 solubilities (20). Base excess (BE) was determined from the measured arterial PCO_2 and pH with a Blood Gas Calculator (26).

Statistical Analyses

Statistical significance ($p < 0.05$) was determined by the Student's t-test, by analysis of variance, or by a non-parametric test of variance (7), as indicated.

RESULTS

After CBx, resting pulmonary ventilation of the goats decreased, as shown in Table 1. Both $\dot{V}_E$ and $\dot{V}_A$ decreased by almost one-fifth

($p < 0.05$). Surprisingly, the mean $\dot{V}_{CO_2}$ was also somewhat diminished, by 11 percent (statistically not significant). Forster et al (11) also observed a decrease in $\dot{V}_{CO_2}$ in chemodenervated goats. $\dot{V}_A$ decreased more than $\dot{V}_{CO_2}$, so that $PaCO_2$ was elevated after CBx, by 3.0 ± 0.6 torr (mean ± S.E., $p < 0.01$). This mild respiratory acidosis did not elicit any detectable renal compensation: arterial-blood pH was lower by 0.027 ± 0.007 units ($p < 0.05$), while BE, $[HCO_3^-]$, and $[Cl^-]$ remained unchanged. Mean PaO_2 was not altered by CBx (Table 1).

In CSF, PCO_2 did not change after CBx, and the small increase in $[HCO_3^-]$ and decrease in $[Cl^-]$ were not statistically significant. CSF pH was unchanged (Table 2).

Table 2

The difference between PCO_2 in CSF and in arterial blood decreased after CBx in all observations (Figure 2). In intact goats, the mean (± S.E.) value for ($P_{CSF}CO_2$ - $PaCO_2$) was 7.0 ± 1.0 torr; after CBx, it was reduced to 4.9 ± 0.3 torr ($p < 0.05$, Wilcoxon test).

Figure 2

Response of the goats to hyperoxic CO_2 rebreathing was altered by CBx. With CB intact, the goats usually became restless to the point that the rebreathing had to be terminated at PET_{CO_2} values around 65 torr. After CBx, the goats tolerated PET_{CO_2} values of 75 - 80 torr with equanimity (Figure 1). While mean slopes of the CO_2 response curves were similar before and after removal of the CB, (Table 3), mean minute ventilation at PET_{CO_2} = 60 torr was reduced from the control value by 42 percent ($p < 0.01$), indicating that position of the CO_2 response curves was shifted to higher PET_{CO_2} values (Figure 3).

Table 3

Figure 3

Ventilatory responses to transitory (5 - 10 min) hypoxia (PaO_2 45 - 60 torr) and hyperoxia (PaO_2 > 300 torr) are summarized in Table 4. These data are based on measurements during control periods when responsiveness to cyanide was tested 3 - 5 weeks and 5 months after CBx (see below). With the CB intact, the goats increased their minute ventilation when acutely hypoxic, on the average by 22 percent; with acute hyperoxia, their mean ventilation decreased by 15 percent. After CBx, pulmonary ventilation was not affected by hypoxia; when hyperoxic, the denervated goats increased their ventilation, on the average by 33 percent.

Ventilatory response to a standardized bolus of cyanide injected into the pulmonary artery is shown in Table 5. When the CB were intact, the goats responded with 4.3 ± 0.4 liters of excess ventilation (see Methods for definition) while hyperoxic (PaO_2 > 300 torr). With acute hypoxia (PaO_2 45 - 60 torr), the response to cyanide bolus was almost doubled ($p < 0.01$). After CBx the response to cyanide was markedly reduced, being just barely detectable on the record of tidal volumes and end-tidal PCO_2. However, computer analysis of these data revealed that three-to-five weeks after CBx the goats still responded with some excess ventilation to cyanide injection. This was significantly less than when the CB were intact ($p < 0.05$ during hyperoxia, $p < 0.01$ during hypoxia). After CBx, the interaction between cyanide injection and acute hypoxia although suggested by the mean values (Table 5), was not statistically significant. Furthermore, the onset of hyperventilation after cyanide injection was delayed when the CB were removed: the mean interval

between time of injection of cyanide into the pulmonary artery and first detectable increase in tidal volume was prolonged by 2.9 seconds ($p < 0.02$). The ventilatory response to cyanide injection five months after CBx was not statistically different from that 3 - 5 weeks after the operation.

DISCUSSION

Acute hypoxia and hyperoxia (of 5 - 10 minutes duration) produced the expected qualitative changes in pulmonary ventilation (31). With CB intact, the goats hyperventilated during acute hypoxia, and decreased their ventilation somewhat during hyperoxia. After CBx, ventilation did not change with acute hypoxia, while hyperoxia produced an increase in ventilation. Stimulation of ventilation by hyperoxia has been reported in chemodenervated dogs (8) and cats (19). The mechanism of this hyperventilation has not been elucidated (19).

The combination of surgical and chemical destruction of the CB did not completely abolish ventilatory responses of the goats to injection of a bolus of cyanide into the pulmonary artery. This was similar to the findings of Forster et al (11) in the same species. It is unlikely that stimulation of the aortic bodies by cyanide was the source of this residual ventilatory response, for several reasons. First, the onset of the response after CBx was delayed by an average of almost 3 seconds. Gonzales et al (14) also found that the latency time in ventilatory response to injection of KCN into the superior vena cava increased by more than 2 seconds after CBx in anesthetized

dogs. Since with resting cardiac output the mean velocity of flow in the central arteries is about 30 cm/sec (6), the structures still responding to cyanide have to be located appreciably farther downstream from the CB. Secondly, in the observations of Forster et al (11), surgical denervation of the aortic chemoreceptors did not abolish the residual ventilatory response to cyanide in goats with excised CB. Finally, if interaction of the cyanide stimulus with hypoxia is characteristic of arterial chemoreceptors (21), our finding of markedly diminished or abolished interaction in denervated goats would suggest that such chemoreceptors are not likely to be involved in the residual ventilatory response to cyanide after CBx. A possible mechanism of ventilatory stimulation by cyanide in the absence of peripheral chemoreceptors could be a direct effect of cyanide on the medullary chemoreceptors, as described in fetal lambs by Jansen and Chernick (15). Cyanide can easily cross the blood-brain barrier by diffusion. The acid dissociation constant of HCN is 7.2×10^{-10} M/l (5); at pH values existing in body fluids, more than 98 percent is in the associated form, which is volatile and lipid-soluble. The delay in onset of hyperpnea after cyanide injection in denervated goats would be compatible with this interpretation. There may be other intracranial sites or mechanisms. Another possibility is that cyanide stimulates ventilation by an extracranial mechanism other than the carotid or aortic chemoreceptors, as proposed by Levine (17). In any case, we conclude that our goats were deprived of peripheral chemoreceptor function after CBx, despite the presence of a vestigial ventilatory response to cyanide. These findings persisted throughout

the 5 months of our observation, in contrast with the observations of Bisgard et al (2) who found in ponies that function of the peripheral chemoreceptors recovered partially after cutting the carotid sinus nerves and stripping the adventitia of the aortic arch; this recovery began 2 months after operation.

The average resting pulmonary ventilation of awake goats was significantly depressed, and $PaCO_2$ elevated after CBx. These findings are in agreement with those of Forster et al (11), and Tenney and Brooks (27) in the same species. Hypercapnia after "peripheral chemodenervation" by excision of the CB or by severing their afferent nerves has also been found in other species, including rat (9), rabbit (4), cat (16, 19), dog (4), and pony (3, 12). Findings in humans have been conflicting: both hypercapnia and normocapnia at rest have been reported in asthmatic humans who underwent bilateral excision of CB (18) and in patients who were "chemodenervated" as a result of bilateral carotid endarterectomy (30).

We found no significant change in pH of cisternal CSF after CBx. This suggests that the input into the "central" chemoreceptors remained the same while the resting ventilation diminished after CBx. Therefore, we conclude with others (3, 4, 8, 9, 11, 12, 16, 19, 27, 30, 31) that the CB contribute significantly to the resting ventilatory drive.

Ablation of the carotid bodies produced a "right shift" of the CO_2 response curves, to higher PCO_2 values; however, slopes of the plots were unchanged. Thus, in spite of hypoventilation at rest, ventilatory responsiveness of the goats to acute hypercapnia was

not diminished by CBx. This is in agreement with findings in awake goats (27) and in anesthetized cats (16). In humans, Wade et al (30) studied the effect of hyperoxic CO_2 inhalation following loss of carotid chemoreceptor function after bilateral carotid endarterectomy. Their findings were also similar to ours; resting $PaCO_2$ was increased after the operation, and CO_2 response curves were shifted to higher PCO_2 levels, with mean (± S.E.) slopes of the plots (reconstructed from Figure 2, l.c.) unchanged: 2.2 ± 0.3 and 2.1 ± 0.4 L/(min x torr) before and after the operation, respectively. On the other hand, Lugliani et al (18) concluded that in asthmatic subjects with resected CB, the increment in ventilation in response to increase in $PaCO_2$ was reduced by 30 percent compared to control subjects. Their patients were not hypercapnic at rest and had normal blood pressures. The authors speculated on the possible role of the "central" chemoreceptors in determining the resting $PaCO_2$ after surgical destruction of the CB. They hypothesized that with carotid endarterectomy or with hypertension caused by loss of baroreceptor function, cerebral perfusion pressure may be increased, and lowering of cerebral-tissue PCO_2 owing to increased cerebral blood flow may decrease the stimulus for the central chemoreceptors, allowing hypercapnia to persist. In our observations, CBx did not produce hypertension or increase variability of blood pressure. While undisturbed and standing quietly in the stanchion, the goats had average systolic/diastolic blood pressures of 119/84 torr (mean ± SD arterial pressure 98 ± 9 torr), and 122/85 torr (mean ± SD arterial pressure 101 ± 6 torr) before and after CBx, respectively. During CO_2 rebreathing, the average (± SD) increase in mean blood pressure was similar before and after CBx, 6 ± 1 and 7 ± 2

torr, respectively. In cisternal CSF, which during normoxia is believed to reflect the ionic composition of the environment of the central chemoreceptors (10), there was no indication of a diminished input: PCO_2 and pH were not different from their values before CBx. Thus, the mechanism proposed by Lugliani et al (18) would not explain the resting hypercapnia in our goats after CBx.

We did not measure cerebral blood flow in our goats, however, the finding of a decrease in the difference in PCO_2 between arterial blood and CSF after CBx suggests, at least qualitatively, that cerebral perfusion was increased in proportion to the cerebral CO_2 production. Role of the CB in the control of cerebral vessels, if any, is controversial (24). Stimulation of the CB with hypercapnia and hypoxia increased CBF in baboons (23), and had no effect in dogs (30). Ablation of the CB reduced cerebral vasodilatation in response to hypoxia and hypercapnia on one study (23) but not in another (1). These experiments involved general anesthesia or complex surgical modification of the vascular anatomy. General anesthesia seems to alter the cerebral vascular responses to stimulation of peripheral chemoreceptors and baroreceptors (29). We are not aware of any direct measurements in intact awake animals or in humans that would have explored vascular responsiveness to hypercapnia (or hypoxia) after peripheral chemodenervation. If cerebral blood flow was indeed higher in our goats after CBx, this could be ascribed to the observed increase in resting $PaCO_2$. Further experiments are needed, with direct measurements of CBF and cerebral-tissue PCO_2 at rest and during CO_2 rebreathing in awake animals, to elucidate whether changes in the regulation of

CBF play any role in the functioning of the central chemoreceptors after peripheral chemodenervation.

The findings that animals and humans deprived of peripheral chemoreceptors hypoventilate at rest, yet respond with an undiminished increase in ventilation to stimulation with CO_2 is intriguing. Phenomenally, this can be categorized as resetting of the controller, while the gain of the controller is unchanged. It would appear from our data that input from the CB influences the set-point of the controller, while the gain, unaffected by CBx, seems to be determined by other mechanisms including central chemoreceptors.

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The views, opinions, and/or findings in this report are those of the authors and should not be construed as an official Department of Army position, policy, or decision, unless so designated by other official documentation.

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References

1. Bates, D., and T.M. Sundt, Jr. The relevance of peripheral baroreceptors and chemoreceptors to regulation of cerebral blood flow in the cat. Circulation Res. 38: 488-493, 1976.

2. Bisgard, G.E., H.V. Forster, and J.P. Klein. Recovery of peripheral chemoreceptor function after denervation in ponies. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 49: 964-970, 1980.

3. Bisgard, G.E., H.V. Forster, J.A. Orr, D.D. Buss, C.A. Rawlings, and B. Rasmussen. Hypoventilation in ponies after carotid body denervation. J. Appl. Physiol. 40: 184-190, 1976.

4. Bouverot, P., and M. Bureau. Ventilatory acclimatization and CSF acid-base balance in carotid chemodenervated dogs at 3550 m. Pflügers Arch. 361: 17-23, 1975.

5. Boxer, G.E., and J.C. Rickards. Chemical determination of vitamin B12. II. The quantitative isolation and colorimetric determination of millimicrogram quantities of cyanide. Arch. Biochem. 30: 372-381, 1951.

6. Burton, A.C. Physiology and Biophysics of the Circulation. Chicago: Year Book Medical Publishers, 1966.

7. Conover, W.J. Practical Nonparametric Statistics. New York: J. Wiley & Sons, 1971.

8. Davenport, H.W., G. Brewer, A.F. Chambers, and S. Goldschmidt. The respiratory responses to anoxemia of unanesthetized dogs with chronically denervated aortic and carotid chemoreceptors and their causes. Am. J. Physiol. 148: 406-416, 1947.

9. Favier, R., and A. Lacaisse. Stimulus oxygène de la ventilation chez le rat éveillé. J. Physiol., Paris 74: 411-417, 1978.

10. Fencl, V., T.B. Miller, and J.R. Pappenheimer. Studies on the respiratory response to disturbances of acid-base balance, with deductions concerning the ionic composition of cerebral interstitial fluid. Am. J. Physiol. 210: 459-472, 1966.

11. Forster, H.V., G.E. Bisgard, and J. P. Klein. Effect of peripheral chemoreceptor denervation on acclimatization of goats during hypoxia. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 50: 392-398, 1981.

12. Forster, H.V., G.E. Bisgard, B. Rasmussen, J.A. Orr, D.D. Buss, and M. Manohar. Ventilatory control in peripheral chemoreceptor-denervated ponies during chronic hypoxemia. J. Appl. Physiol. 41: 878-885, 1976.

13. Gabel, R.A. Algorithms for calculating and correcting blood-gas and acid-base variables. Respir. Physiol. 42: 211-232, 1980.

14. Gonzales, F., Jr., W.E. Fordyce, and F.S. Grodins. Mechanism of respiratory responses to intravenous $NaHCO_3$, HCl, and KCN. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 43: 1075-1079, 1977.

15. Jansen, A.H., and V. Chernick. Respiratory response to cyanide in fetal sheep after peripheral chemodenervation. J. Appl. Physiol. 36: 1-5, 1974.

16. Katsaros, B. Die Rolle der Chemoreceptoren des Carotisgebiets der narkotisierten Katze für die Antwort der Atmung auf isolierte Änderung der Wasserstoffionen-Konzentration und des CO_2-Drucks

des Blutes. Pflügers Arch. 282: 157-178, 1965.

17. Levine, S. Nonperipheral chemoreceptor stimulation of ventilation by cyanide. J. Appl. Physiol. 39: 199-204, 1975.

18. Lugliani, R., B.J. Whipp, C. Seard, and K. Wasserman. Effect of bilateral carotid-body resection on ventilatory control at rest and during exercise in man. N. Engl. J. Med. 285: 1105-1111, 1971.

19. Miller, M.J., and S.M. Tenney. Hyperoxic hyperventilation in carotid-deafferented cats. Respir. Physiol. 23: 23-30, 1975.

20. Mitchell, R.A., D.A. Herbert, and C.T. Carman. Acid-base constants and temperature coefficients for cerebrospinal fluid. J. Appl. Physiol. 20: 27-30, 1965.

21. Ott, N. Die Wirkung von Natriumcyanid auf die Chemoreceptoren des Carotissinusgebiets. Zschft. Biol. 114: 59-80, 1963.

22. Pappenheimer, J.R., S.R. Heisey, E.F. Jordan, and J. DeC Downer. Perfusion of the cerebral ventricular system in unanesthetized goats. Am. J. Physiol. 203: 763-774, 1962.

23. Ponte, J., and M.J. Purves. The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels. J. Physiol., London. 237: 315-340, 1974.

24. Purves, M.J. The Physiology of the Cerebral Circulation. Cambridge: University Press, 1972, pp 276-278.

25. Read, D.J.C. A clinical method for assessing the ventilatory response to carbon dioxide. Australas. Ann. Med. 16: 20-32, 1967.

26. Severinghaus, J.W. Blood gas calculator. J. Appl. Physiol. 21: 1108-1116, 1966.

27. Tenney, S.M., and J.G. Brooks. Carotid bodies, stimulus interaction, and ventilatory control in unanesthetized goats. Respir. Physiol. 1: 211-224, 1966.

28. Traystman, R.J., R.S. Fitzgerald, and S.C. Loscutoff. Cerebral circulatory responses to arterial hypoxia in normal and chemodenervated dogs. Circulation Res. 42: 649-657, 1978.

29. Vatner, S.F., L.L. Priano, J.D. Rutherford, and W.T. Manders. Sympathetic regulation of the cerebral circulation by the carotid chemoreceptor reflex. Am. J. Physiol. 238: H594-H598, 1980.

30. Wade, J.G., C.P. Larson, Jr., R.F. Hickey, W.K. Ehrenfeld, and J.W. Severinghaus. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N. Engl. J. Med. 282: 823-829, 1970.

31. Watt, J.G., P. Dumke, and J.H. Comroe, Jr. Effects of inhalation of 100 percent and 14 percent oxygen upon respiration of unanesthetized dogs before and after chemoreceptor denervation. Am. J. Physiol. 138: 610-617, 1943.

TABLE 1

Pulmonary ventilation and composition of arterial blood in awake goats, before and 3 - 5 weeks after ablation of carotid bodies.

Carotid bodies	$\dot{V}_E$ l/min BTPS	$\dot{V}_A$ l/min BTPS	$\dot{V}_{CO_2}$ ml/min STPD	$PaCO_2$ torr	PaO_2 torr	pH	BE mE/l	$[HCO_3^-]$ mM/l	$[Cl^-]$* mM/l
Intact	10.8±.7	5.1±.2	212±10	36.5±1.0	88.1±5.8	7.423±.004	-.7±.4	23.2±.4	112±2
Ablated	8.8±.3	4.2±.2	189± 9	39.2± .7	89.8±4.7	7.397±.004	-1.1±.7	23.2± 6	112±1
t-test (paired samples)									
p	<.05	<.05	NS	<.01	NS	<.05	NS	NS	NS

Values are means ± S.E. of repeated measurements in 5 goats. *Data on 4 goats.

TABLE 2

Composition of cerebrospinal fluid in awake normoxic goats, before and 3 - 5 weeks after ablation of carotid bodies.

Carotid bodies	PCO_2 torr	pH	$[HCO_3^-]$ mM/l	$[Cl^-]$ mM/l
Intact	44.4±1.2	7.306±.013	23.7±.4	132±1
Ablated	44.6±0.6	7.307±.011	24.8±.5	130±1
t-test (paired samples)	NS	NS	NS	NS

Values are means ± S.E. of repeated measurements in 4 goats.

TABLE 3

Effect of ablation of carotid bodies on the ventilatory response to hyperoxic CO_2 rebreathing.

Carotid bodies	Slope of CO_2 response curves L/(min x torr)	$\dot{V}_E$ at P_{ETCO_2} = 60 torr L/min., BTPS
Intact	3.5 ± .4	29.5 ± 6.7
Ablated	2.9 ± .3	17.3 ± 2.6
t-test (paired samples)	NS	$p < 0.01$
Wilcoxon test	NS	

Values are means ± S.E. of repeated measurements in 4 goats. PaO_2 > 300 torr.

TABLE 4

Ventilatory response to acute hypoxia and hyperoxia in goats before and after ablation of carotid bodies.

	$\dot{V}_E$, liters/minute, BTPS		
Carotid bodies	Normoxia PaO_2 85-95	Hypoxia PaO_2 45-60	Hyperoxia PaO_2 > 300
Intact	11.7±1.9	14.3±1.6*	9.9±0.7
Ablated	10.8±1.1	11.3±0.9	13.8±1.2†

Analysis of variance:

* Significantly different from normoxia and hyperoxia in intact goats ($p < 0.05$), and from hypoxia in denervated goats ($p < 0.05$).

† Significantly different from normoxia and hypoxia in denervated goats ($p < 0.05$), and from hyperoxia in intact goats ($p < 0.05$).

TABLE 5

Ventilatory response to injection of a bolus of cyanide (1 μM/kg) into pulmonary artery.

	Integrated Excess Ventilation (liters, BTPS)		Interval between injection and onset of response (sec)
Carotid bodies	Hyperoxia (PaO_2 > 300 torr)	Hypoxia (PaO_2 45-60 torr)	
Intact	4.3 ± 0.4	8.1 ± 0.6	8.4 ± 0.4
Ablated			11.1 ± 1.0*
3 - 5 weeks	1.7 ± 0.7	2.8 ± 0.8†	
5 months	2.2 ± 0.4	2.8 ± 0.6†	

Analysis of variance: Intact goats differ from denervated goats in hypoxia ($p < 0.01$ and hyperoxia ($p < 0.05$). In intact goats, the response in hypoxia is greater than in hyperoxia ($p < 0.01$). In denervated goats, the responses in hypoxia and hyperoxia are not significantly different; the responses 3 - 5 weeks and 5 months after denervation are not significantly different.

* $p < 0.02$ (t-test)

† Not significantly different from values in hyperoxia in denervated goats by non-parametric ranking test (7).

Values are means ± S.E. of repeated measurements in 5 awake goats.

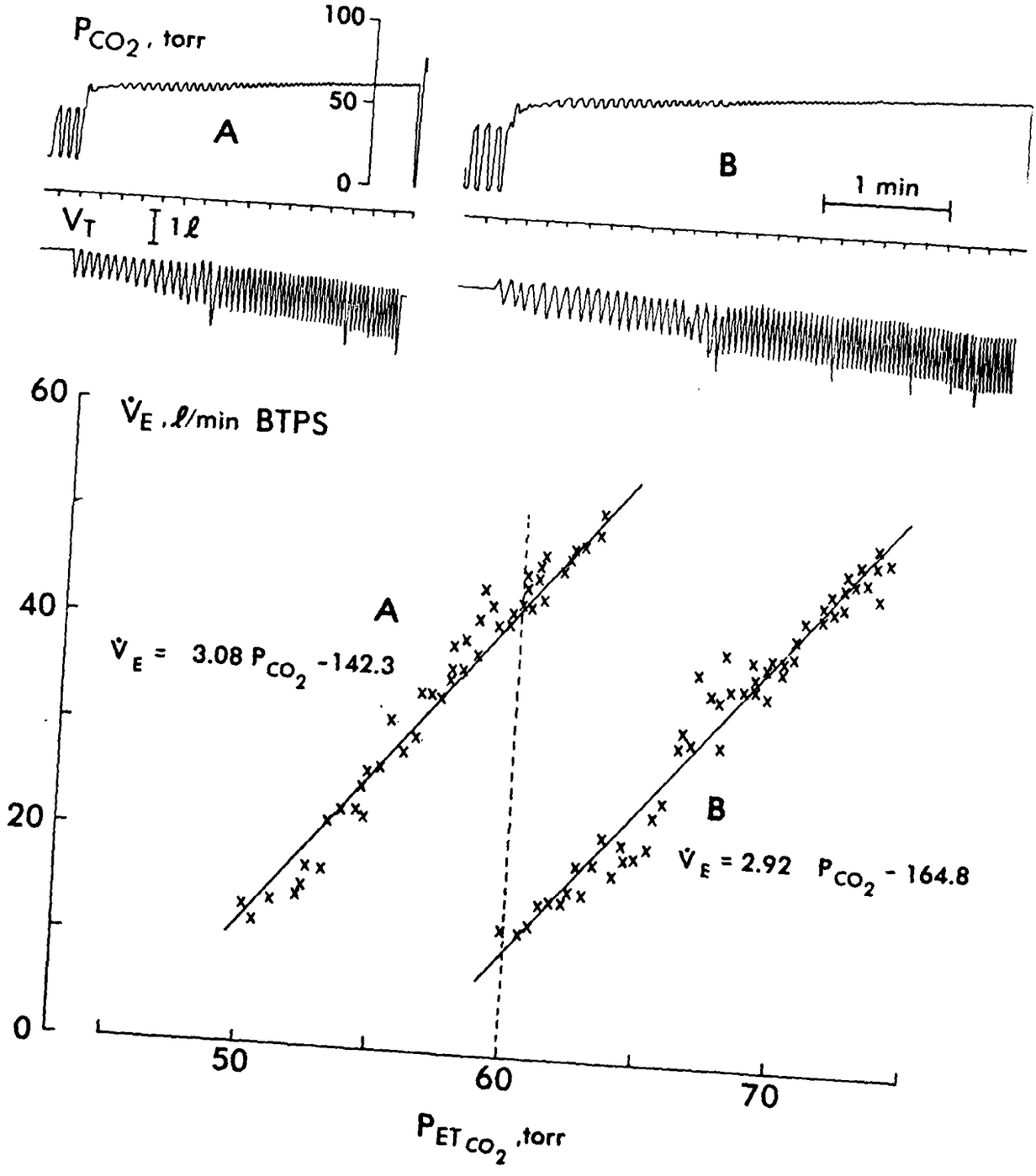
LEGENDS TO FIGURES

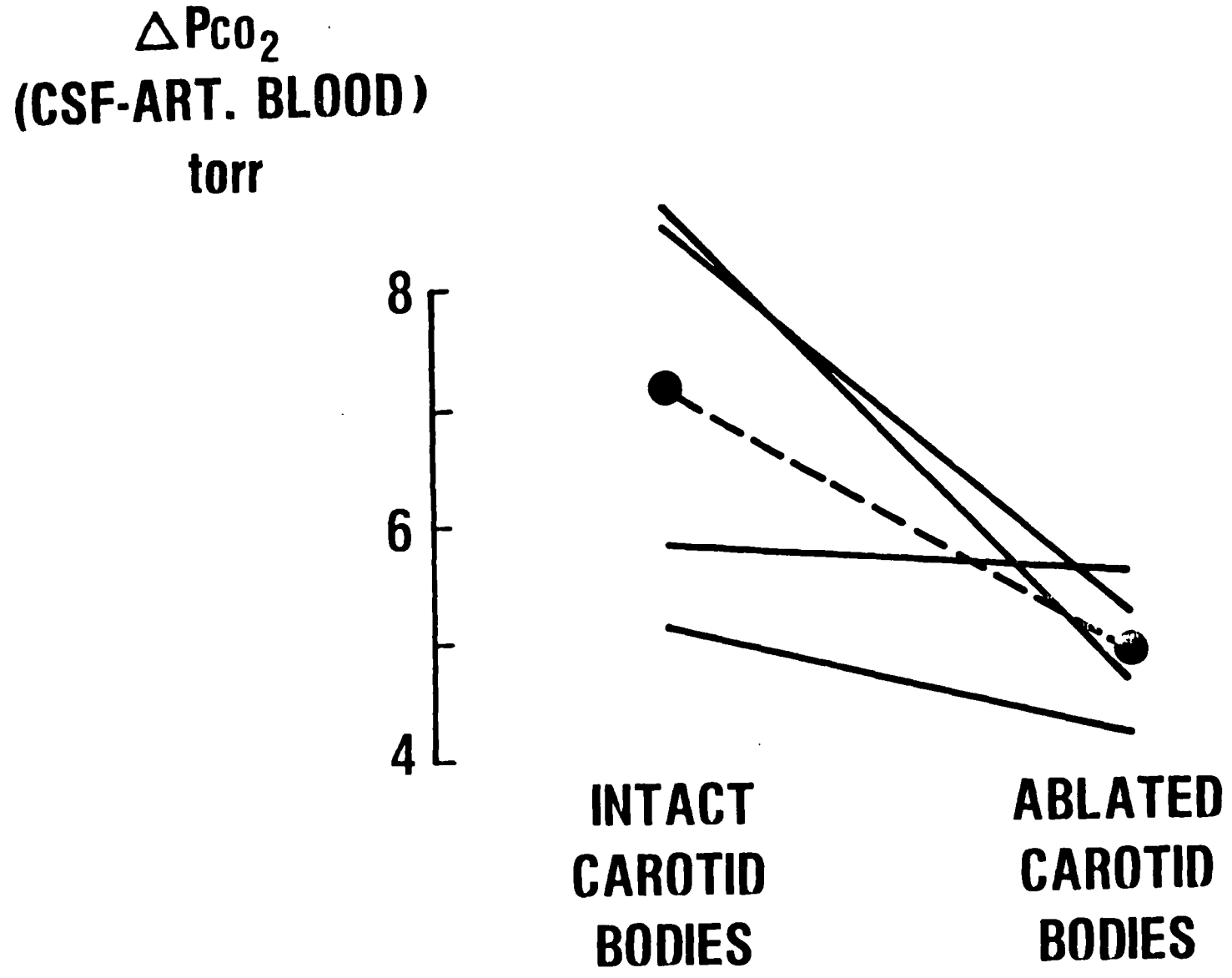
Figure 1. Hyperoxic (PaO_2 > 300 torr) CO_2 rebreathing in goat SP before (A) and after (B) ablation of carotid bodies. Top panel: record of PCO_2 at the airway and tidal breathing (V_T). Bottom panel: plot of expired minute ventilation ($\dot{V}_E$), derived by computer breath-by-breath, against end-tidal PCO_2 ($P_{ET}CO_2$). Least-square regressions of the plots are given. The vertical dotted line indicates $\dot{V}_E$ at P_{ET} = 60 torr (see text). In A, rebreathing was terminated at $P_{ET}CO_2$ < 65 torr because the goat became restless. In B, the goat tolerated increase in $P_{ET}CO_2$ to almost 75 torr with equanimity.

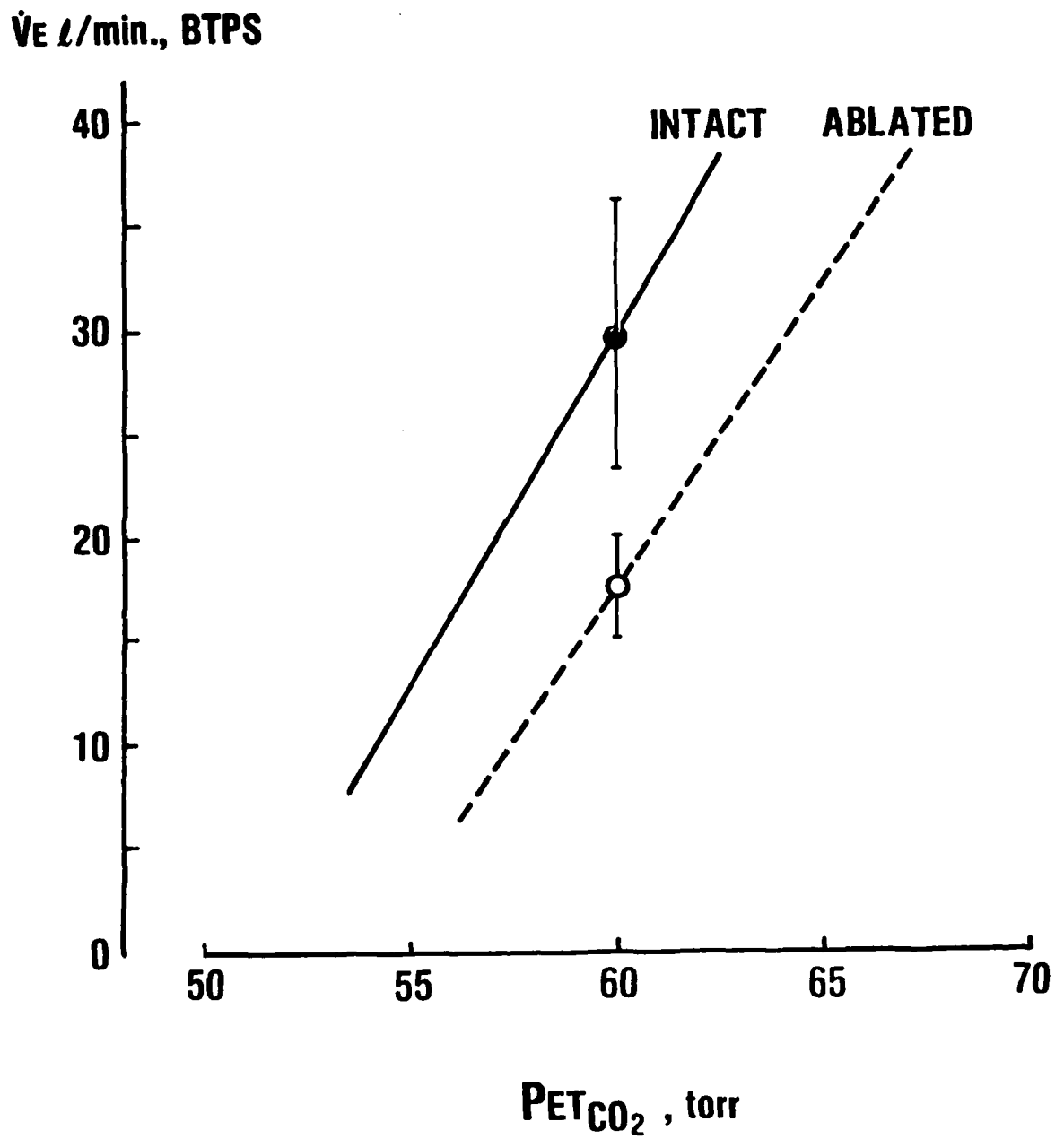
Figure 2. Effect of ablation of the carotid bodies on the difference in PCO_2 between CSF and arterial blood. The points joined by a broken line indicate mean values.

Figure 3. Mean ventilatory responses to hyperoxic (PaO_2 > 300 torr) CO_2 rebreathing, constructed from the mean (± S.E.) values of expired minute ventilation ($\dot{V}_E$) at end-tidal PCO_2 ($P_{ET}CO_2$) of 60 torr, and from mean values of the slopes of the plots of $\dot{V}_E$ vs $P_{ET}CO_2$. See Table 3 for numerical data.

VENTILATORY RESPONSE TO CO_2 REBREATHING IN A GOAT (SP # 1)
BEFORE (A) AND AFTER (B) ABLATION OF CAROTID BODIES.




ΔPco2
(CSF-ART. BLOOD)
torr
8
6
4
INTACT
CAROTID
BODIES
ABLATED
CAROTID
BODIES


V̇E ℓ/min., BTPS
40
30
20
10
0
INTACT
ABLATED
50
55
60
65
70
PETCO2 , torr

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