Enhancement of Cerebrovascular Effect of CO₂ by Hypoxia

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SUMMARY Internal carotid blood flow, taken as an index of cerebral blood flow (CBF); arterial pressure; and respiratory O₂ and CO₂ concentrations, were measured in halothane (1%)-anesthetized, paralyzed and mechanically ventilated rabbits. CBF was determined at end-tidal CO₂ of 4% (normocapnic) and 8%, as inspired O₂ ([O₂]) was varied stepwise over the range of 6.5 to 92%. Normocapnic CBF was constant over the range of 15 to 92% [O₂], but it increased significantly to 240% and 380% of control when [O₂] was at 10% and 6.5%, respectively. Cerebrovascular response to CO₂ was constant over the range of [O₂], tested, except for a significant elevation to 180% of control at [O₂] of 10%.

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CEREBRAL BLOOD FLOW (CBF) is well known to increase under the influence of hypercapnia and hypoxia. A continuous, roughly linear relationship exists over a wide range between CBF and arterial PCO₂, while the effect of lowered arterial PO₂ is seen only at some threshold level below which CBF is inversely related to PaO₂.

The combined effect of hypoxia and hypercapnia has been given much less attention than their separate actions. Lennox and Gibbs examined the effect of different combinations of inspired gas concentrations of O₂ and CO₂ on CBF, but their results have to be interpreted with caution since they estimated CBF from the arteriovenous difference of O₂ while assuming a constant cerebral O₂ consumption. More recently, the question has been reexamined by Shapiro et al. who studied the effects of combined hypoxia and hypercapnia on CBF in man. Although these authors did not provide control values of CBF in their subjects under 5% CO₂ without hypoxia, they did find higher values for CBF under 10% O₂–5% CO₂ than had been reported by other authors for 5% CO₂ alone. Furthermore, Flohr et al. have reported that the action of hypoxia on CBF in cats was enhanced by hypercapnia.

While it thus appears that an interaction may exist between the effects on CBF of hypoxia and hypercapnia, the quantitative aspects of the interaction between O₂ and CO₂ over a broad range, including hyperoxic levels, have not been studied. Moreover, while it is generally, but not unanimously, accepted that an increase in PaO₂ from 50 mm Hg to one atmosphere has negligible effect on CBF at normocapnia, the possible effect of hypoxia on CBF reactivity to CO₂ has not been explored.

Materials and Methods

Adult male rabbits, 2.5–3.0 kg, were anesthetized with 4% halothane, paralyzed with pancuronium (0.6 mg/hr) and mechanically ventilated. Following induction, animals were maintained on 1% halothane in 40% O₂–60% N₂ throughout each experiment. A femoral artery was cannulated for recording of mean arterial pressure (MAP) and for withdrawal of blood samples for analysis. The external carotid artery and any extracranial branches of the internal carotid artery were ligated, and a cuff-type electromagnetic flow probe (Biotronex) was placed on the common carotid artery for measurement of internal carotid blood flow (ICBF). A hydraulic occluder was applied to the carotid artery, distal to the flow probe, to allow determination of zero flow. Body temperature was monitored with a rectal thermometer and maintained at 38°C with radiant heat. An isotonic solution of sodium bicarbonate, pH 7.44 (1.26 mg/100 ml), was injected i.v. at 6.5 ml/kg/hr to maintain pH and replace fluid loss. Respiratory O₂ and CO₂ were monitored at the tracheal airway by Beckman OM-11 and LB-2 analyzers, respectively, and continuously recorded. Arterial Po₂, Pco₂ and pH were determined on a Radiometer 3M5 MK2 blood gas analyzer.

In each experiment ICBF, MAP, and respiratory O₂ and CO₂ were continuously monitored and expressed as percent. Regulation of the composition of inspired gas was accomplished by adjusting the proportions of O₂, N₂ and CO₂ delivered through calibrated flowmeters, with total gas flow maintained constant. Initially the animal was ventilated so as to achieve constant "normocapnic" end-tidal CO₂ ([CO₂]ₜₚ) of approximately 4% (range: 3.8–4.4%; average PaCO₂ = 33 ± 1 (SE) mm Hg; average pH = 7.39) and inspired O₂ concentration ([O₂]) of 40% (PaO₂ = 147 ± 6 (SE) mm Hg). After stabilization, [CO₂]ₜₚ was elevated to 8% (range: 8.0–8.8%; average PaCO₂ = 52 ± 3 (SE) mm Hg; average pH = 7.23) until ICBF reached a new steady level (3–4 min) and [CO₂]ₜₚ was then returned to its original level: [O₂]; was maintained constant during the change in [CO₂]ₜₚ. The same procedure was repeated at [O₂]; of 6.5, 10, 15, 20 and 92%, corresponding to PaO₂ (± SE) 24 ± 2, 30 ± 3, 43 ± 5; 63 ± 4, 147 ± 6, 356 ± 15 mm Hg, respectively. At each level of [O₂]; and [CO₂]ₜₚ, an arterial blood sample was obtained for analysis.

One to three measurements of ICBF were made at each level of [CO₂]ₜₚ and [O₂];. These data were used to calculate the regression equation of ICBF on [CO₂]ₜₚ by the least-squares method for each
animal. CO₂ reactivity (CO₂R) was defined as the coefficient (slope) of that equation. To cancel out variations between animals, ICBF and CO₂R were normalized. Normalized ICBF (ICBFₙ) was expressed as a percentage of the value of ICBF at [CO₂ET] 4% and [O₂I] 40%. Normalized CO₂R (CO₂Rₙ) was expressed as a percentage of the value of CO₂R at [O₂I] 40%. An average of ICBFₙ at normocapnia ([CO₂I] 4%) and an average of CO₂Rₙ obtained from all animals were calculated for each [O₂I] level. Analysis of variance with repeated measures was performed to test for differences between means.

Results

Figure 1 illustrates a representative experiment in which an increase in [CO₂I]ET from 4% to 8%, at [O₂I] 40%, resulted in an increase in ICBF which reached a new level within approximately 3 min. In this case ICBF increased by 40%, yielding a calculated CO₂ reactivity of 10, i.e. 10% increase in ICBF for each percent change in [CO₂I]ET. Figure 2 depicts the increase in ICBF accompanying reduction of [O₂I] from 40 to 10%, in the same experiment as figure 1. ICBF increased promptly, reaching 230% of control in 3 min. During this period of hypoxia, an increase in [CO₂I]ET from 4 to 8% resulted in a further, considerably faster, increase of 80% of control ICBF to a final value of 310%. This yielded a CO₂ reactivity of 20, i.e. 200% of the reactivity at [O₂I] 40%; this value was close to the group mean of 180% for CO₂Rₙ as shown in figure 3b, which presents the combined results of all nine experiments. ICBFₙ remained essentially constant over the range of [O₂I] 15-92% (fig. 3a).

Changes in MAP that accompanied variations in [CO₂I]ET or [O₂I] were generally negligible, as in figures 1 and 2.

Discussion

The results confirm the observation of others¹⁻⁴ that CBF under normocapnia increases markedly as Pao₂ decreases below approximately 50 mm Hg ([O₂I] 15%). The maximum CBF attained, approximately
400 percent of control, was reached at the lowest \([O_2]_i\) tested, i.e. 6.5%. The magnitude of response was lower than in some reports, but higher than in others, but the possible effects of species characteristics, type and depth of anesthesia, extent of control of ventilation, and differences in methodology are too complex to allow specific explanation of these variations. As far as we are aware, no observations of this sort have been made in rabbits. Throughout the normoxic and hyperoxic range, \([O_2]_i\) of 20-92\% (Pao\(_2\) 63-356 mm Hg), CBF was constant, again coinciding with previous reports.

At any given \([O_2]_i\), imposition of hypercapnia ([CO\(_2\)]_i \(\geq 8\%\)) significantly increased blood flow by a mean of 40\% of the normoxic normocapnic CBF, except at \([O_2]_i\) 10\% (Pao\(_2\) = 30 mm Hg), where the increase amounted to 80\% (figs. 1 and 2). This doubling of the effect of CO\(_2\) is expressed by the corresponding increase in normalized CO\(_2\) reactivity (CO\(_2\)R\(_n\)) at \([O_2]_i\) 10\%, with a tendency toward increase at \([O_2]_i\) 15\%, as shown in figure 3b. No changes in CO\(_2\)R occurred in the hyperoxic range. In other words, the effects of hypoxia and hypercapnia were additive, except at \([O_2]_i\) 10\% where a greater additive response occurred, showing that the two effects potentiate each other. This confirms, in general, the findings of Lennox and Gibbs, Shapiro et al., and Flohr et al., but with extension to the combined effect of hypercapnia and several levels of hypoxia and hyperoxia.

The reduction of CO\(_2\)R back to control level at \([O_2]_i\) 6.5\% in the face of a continuing rise in ICBF\(_n\) may reflect the achievement of maximum CBF at this level of Pao\(_2\). Alternatively, it may result from an interference by deep hypoxia with the basic mechanism mediating the cerebral vasodilation induced by hypercapnia.

The rabbit has an advantage over most laboratory animals for the study of CBF because the internal carotid artery in this species supplies only cerebral tissue in its intracranial course. Thus, measurement of flow in this artery allows a continuous estimate of CBF. Since the level of anesthesia can significantly affect both CBF and CO\(_2\) reactivity, except of an inhalation agent, such as halothane in our experiments, allows precise control of effective concentration of the anesthetic, particularly when ventilation is maintained constant. The ventilatory control also permits study of the vascular effects of hypoxia and hypercapnia, independent of indirect actions via alterations of ventilation.

Although the cerebrovascular effect of asphyxia was already known a century ago, we have not advanced in its understanding beyond a characterization of the separate effects of hypoxia and hypercapnia. The mechanisms of these responses remain obscure. The interpretation prevalent for many years, that a decrease in brain extracellular pH due to lactic acidosis determines the hypoxic vasodilatation, has been contested by recent reports. The role of pH as the sole determinant of hypercapnic cerebral vasodilatation also has been challenged by the findings that brain stem lesions and atropine can block this response, which is considerably enhanced by physostigmine, a cholinesterase inhibitor. These observations have suggested the involvement of neurogenic mechanisms in the cerebrovascular effects of blood \(O_2\) and CO\(_2\). A comparison of the effects of \(O_2\) and CO\(_2\) on CBF with those on ventilation, an obviously neurally mediated response, might be pertinent. As has been reported previously and as is confirmed here, CBF does not change when Pao\(_2\) is in the range of around 700 to 50 mm Hg, but increases very steeply in inverse proportion to Pao\(_2\) when the latter is below 50 mm Hg (fig. 3). The response of ventilation to Pao\(_2\) closely parallels this, showing a "threshold" at 50-60 mm Hg Pao\(_2\) and a negative relation with Pao\(_2\) below this.

The present study reveals that CBF reactivity to CO\(_2\) is affected only when Pao\(_2\) is reduced below 50 mm Hg. The same has been observed for the effect of Pao\(_2\) on the relationship of ventilation to Paco\(_2\). In both cases, this increased response to CO\(_2\) suggests an effect of Pao\(_2\) on the basic mechanism that relates Paco\(_2\) to ventilation or to CBF, as opposed to a simple additive effect.

Aside from its resemblance to the ventilatory response, the enhancement of the cerebrovascular effect of CO\(_2\) induced by hypoxia is a phenomenon that deserves further exploration. It would be interesting to assess the role of peripheral chemoreceptors and decerebration in this response, as well as the effects of cholinergic blocking drugs, all of which have been shown, as stated above, to affect CO\(_2\) reactivity under normoxia. Understanding of the nature of the interaction of these basic cerebrovascular reactions may ultimately help in the management of clinical situations in which hypoxia may coexist with either hyper- or hypocapnia.

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