Hypoxic Ventilatory Response in Subjects with Normal and High Oxygen Affinity Hemoglobins

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ABSTRACT It has still not been shown unequivocally whether a decrement of arterial oxygen content or tension governs the ventilatory response to hypoxia. In an attempt to discriminate between the two possibilities, we have measured the ventilatory response to isocapnic progressive hypoxia in two healthy children with a high oxygen affinity hemoglobin (Hb Andrew-Minneapolis) and in their age- and sex-matched normal siblings. Hypoxic ventilatory response was identical in all subjects, there being no difference in minute ventilation at $P_{A_{O_2}}$ = 40 mm Hg or in k (decrement of P_{O_2} required to increase ventilation by a factor of 2.718). In contrast, at $P_{A_{O_2}}$ = 40 mm Hg, hemoglobin oxygen saturation decreased markedly in controls but only slightly in high affinity subjects. Furthermore, the increase in heart rate at $P_{A_{O_2}}$ = 40 mm Hg was significantly less in high affinity subjects, suggesting a concomitant difference in oxygen delivery. Thus, with identical decrements in $P_{A_{O_2}}$ but widely divergent changes in arterial oxygen content and oxygen delivery, controls and high affinity subjects showed virtually identical ventilatory response to hypoxia. We conclude that decrements of oxygen tension are the major stimulus for hypoxic ventilatory response.

INTRODUCTION

The ventilatory response to hypoxia is mediated through the carotid body's chemoreceptors, but it has not yet been shown unequivocally whether the stimulus is a decrement of arterial oxygen content (CaO_2) or tension (PaO_2).[1] Although the weight of evidence favors the latter as the regulatory factor (1, 2), there have been inherent difficulties in all experimental models used thus far (*vide infra*). Since at least one oxygen-responsive system (erythropoietin production) appears to depend upon CaO_2 (3), the problem remains of interest, and the search has continued for a model that can definitively distinguish the effects of PaO_2 and CaO_2 on the carotid body. It occurred to us that humans with a high oxygen affinity hemoglobin (Hb) would provide such a model. Consequently, we have studied hypoxic ventilatory response in a family with Hb Andrew-Minneapolis, a stable beta-chain mutant Hb with high oxygen affinity (whole blood $P_{50} \simeq 17$ mm Hg), and an oxygen dissociation curve of normal shape (4).

This report was presented in preliminary form at the American Federation for Clinical Research meeting in Washington, D. C. in May 1977.

Received for publication 11 April 1977 and in revised form 8 August 1977.

[1] *Abbreviations used in this paper*: CaO_2, arterial oxygen content; Hb, hemoglobin; HbO_2, hemoglobin oxygen saturation; ΔHR, increase in heart rate; P_{CO_2}, pressure of carbon dioxide; P_{O_2}, pressure of oxygen; PaO_2, arterial oxygen tension; $P_{A_{CO_2}}$, alveolar P_{CO_2}; $P_{A_{O_2}}$, alveolar P_{O_2}; $\Delta\dot{V}_I$, incremental ventilation.

TABLE I

*Ventilatory Response to Hypoxia and Hypercapnia in Subjects with Normal (N) and High (H) Oxygen Affinity Hemoglobins**

Subject	Age	Sex	P_{50}	Hb	TLC	FEV_1	FEF_{25-75}	Hypoxia					Hypercapnia	
								PA_{CO_2}	$\dot{V}_{40}$	k	$HbO_{2_{40}}$	ΔHR	S	B
	yr		*mm Hg*	*g/dl*	*liters*	*liters*	*liters/s*	*mm Hg*	*liters/min*	*mm Hg*	*%*	*%*	*liters/min/mm Hg*	*mm Hg*
N1	13	M	26.9	13.0	3.4 (87)‡	2.4 (92)‡	3.0 (97)‡	38	19	24	73	18 (76)§	3.1	39
N2	16	F	27.0	13.2	3.8 (100)	2.6 (90)	3.2 (100)	37	21	28	73	47 (76)	2.0	37
H1	12	M	17.0	16.0	3.2 (84)	2.3 (92)	3.2 (107)	39	18	26	89	7 (108)	3.0	35
H2	18	F	17.2	16.8	3.7 (95)	2.8 (88)	3.8 (95)	37	24	27	90	10 (98)	2.1	33

* *Abbreviations*: N, normal oxygen affinity; H, high oxygen affinity; P_{50}, whole blood P_{50} (normal, 27.0±1.0 mm Hg); TLC, total lung capacity; FEV_1, forced expiratory volume in 1 second; FEF_{25-75}, maximum mid-expiratory flow rate; PA_{CO_2}, alveolar P_{CO_2} maintained throughout study; $\dot{V}_{40}$, absolute ventilation at PA_{O_2} = 40 mm Hg; k, decrement in P_{O_2} required to increase ventilation by a factor of 2.718; $HbO_{2_{40}}$, arterial Hb oxygen saturation at PA_{O_2} = 40 mm Hg; ΔHR, increase in heart rate at PA_{O_2} = 40 mm Hg vs. PA_{O_2} = 100 mm Hg; S, slope of P_{CO_2} response line; B, intercept of P_{CO_2} response line on P_{CO_2} axis.

‡ Number in parentheses is the percentage of predicted value.

§ Number in parentheses: absolute heart rate (beats per minute) at PA_{O_2} = 100 mm Hg.

METHODS

Subjects. The subjects were all healthy, nonsmoking children with normal pulmonary function (Table I). The abnormals, H1 (12-yr-old male) and H2 (18-yr-old female), had low P_{50}s and elevated Hb concentrations for age. Their normal siblings, N1 (13-yr-old male) and N2 (16-yr-old female) had normal P_{50}s and Hb concentrations for age. At onset of testing, mean venous bicarbonates were 24.9 meq/liter and 23.6 meq/liter for normal and high affinity subjects, respectively. Informed, signed consent was obtained.

Isocapnic hypoxic ventilatory response. A detailed description of the method has appeared elsewhere (5). Briefly, subjects rebreathed from a closed system containing a variable CO_2 absorber bypass and a recording spirometer. End-tidal P_{CO_2} (PA_{CO_2}) and P_{O_2} (PA_{O_2}), tidal volume, and heart rate were continuously recorded as the PA_{O_2} was lowered from 120 to 40 mm Hg over 4–5 min; PA_{CO_2} was kept at each subject's resting level. Two response tests were done on each subject with an intervening rest period. Ventilation was measured by averaging tidal volume over five breaths at each 10-mm Hg decrement of PA_{O_2}. The relationship between incremental ventilation ($\Delta\dot{V}_I$) and P_{O_2} at constant P_{CO_2} is expressed by $\Delta\dot{V}_I = \Delta\dot{V}_0 e^{-(P_{O_2}/k)}$, where k is the decrement in P_{O_2} required to increase ventilation by a factor of e (2.718), and $\Delta\dot{V}_0$ is the intercept at P_{O_2} = 0. Regression of the logarithm of $\Delta\dot{V}_I$ against P_{O_2} was computed.

Hypercapnic ventilatory response. Ventilatory response to hypercapnia was determined by a rebreathing method (6). Subjects rebreathed from a bag (5% CO_2 in O_2) for 4 min or until PA_{CO_2} = 65 mm Hg; PA_{O_2} was greater than 200 mm Hg at all times. Two response tests were done on each subject. Ventilation was measured as above. The relationship between ventilation and P_{CO_2} is $\dot{V}_I = S(P_{CO_2} - B)$, where B is the P_{CO_2} at $\dot{V}_I$ = O, and S is the slope of the CO_2 response line (7). Constants were obtained by linear regression of $\dot{V}_I$ on P_{CO_2}.

Oxygen content. During hypoxic response tests, Hb oxygen saturation (HbO_2) was continuously monitored with a standardized Hewlett-Packard (Hewlett-Packard Co., Palo Alto, Calif.) 47201A ear oximeter.[2] CaO_2 was calculated from measured Hb and HbO_2, assuming PA_{O_2} to equal PaO_2.

RESULTS

Ventilatory response to hypercapnia. Ventilatory response to hypercapnia was the same for normal and high affinity subjects (Table I); there was no significant difference in S (slope of response curve) or B (intercept of response curves on PA_{CO_2} axis).

Ventilatory response to progressive isocapnic hypoxia. Individual curves of ventilatory response to hypoxia as a function of PA_{O_2} revealed no difference between normal and high oxygen affinity subjects (Fig. 1A). There was no difference between normal and high oxygen affinity subjects in $\dot{V}_{40}$ or in k (Table I).

Oxygen content and delivery. In contrast, when ventilatory response to hypoxia is plotted as a function of HbO_2, there is a clear divergence between normals and abnormals (Fig. 1B), reflecting the marked difference in degree of arterial desaturation between the two groups during progressive hypoxia. At PA_{O_2} = 40 mm Hg, normals reached a HbO_2 of 73% while

[2] This device was standardized against arterialized capillary blood and an internal standard. In view of the spectral normality of oxy- and deoxy-Hb Andrew-Minneapolis, we anticipated that the oximeter would yield reliable values. The validity of the device was further confirmed by the virtual identity between the HbO_2 values obtained by oximeter and those mathematically predicted (based on measured PA_{O_2} and the known position and shape of the oxygen dissociation curves for each subject).

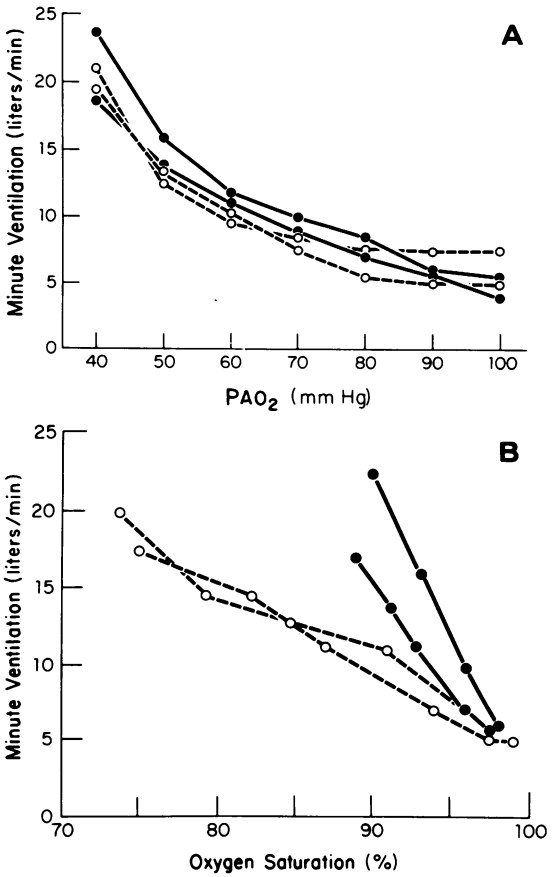

FIGURE 1 Ventilatory response to isocapnic progressive hypoxia. Subjects are siblings from a single family with Hb Andrew-Minneapolis; two have high oxygen affinity (● ——●), and two have normal oxygen affinity (○ - - - ○). (A) As a function of PA_{O_2}, hypoxic ventilatory response is identical in all subjects. (B) As a function of arterial oxygen saturation, ventilatory response of normal and high affinity subjects diverges, reflecting a marked difference in degree of arterial desaturation during progressive hypoxia. Correlation coefficients for all curves are 0.9 or greater.

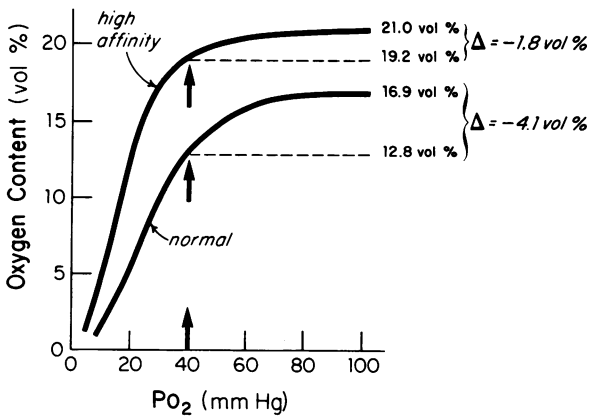

FIGURE 2 Arterial oxygen content and potential oxygen delivery. Curves are derived from arterial oxygen saturations measured during hypoxic response testing. The upper curve is that for high affinity subject H1; the lower curve is for normal subject N1. Under hypothetical normal conditions of PaO_2 = 100 mm Hg and end-capillary PO_2 = 40 mm Hg (arrow), the high affinity subject has an oxygen delivery deficit with an oxygen unloading (Δ=) of only 1.8 vol % as compared to 4.1 vol % for the normal subject. However, under conditions of marked hypoxia so that PaO_2 = 40 mm Hg (arrow), the high affinity subject has much greater oxygen loading (19.2 vs. 12.8 vol %) and much more oxygen potentially available for tissue delivery.

the high affinity subjects desaturated only to a mean of 89.5%, confirming a marked difference in oxygen available for delivery (in favor of high affinity subjects; see Fig. 2). In addition, the increase in heart rate (ΔHR) for high affinity subjects at PA_{O_2} = 40 mm Hg was significantly less than expected (Table I, Fig. 3).

DISCUSSION

Other investigators have attempted to determine whether a decrement of PaO_2 or CaO_2 stimulates the carotid body. Unfortunately, none of the experimental models used thus far has been free of major difficulties.

Models employing induced carboxyhemoglobinemia have yielded conflicting results (8–11). Furthermore, exposure to carbon monoxide is known to affect cardiac output, cerebrospinal fluid chemistry, and the central respiratory control centers (11). Finally, carbon

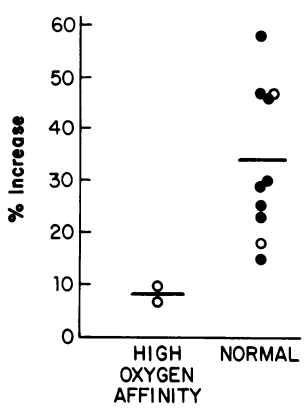

FIGURE 3 Increase of heart rate during hypoxic response testing. Heart rate is expressed as percentage increase at PA_{O_2} = 40 mm Hg over that at PA_{O_2} = 100 mm Hg. Subjects reported herein are indicated by open circles (○). Eight normal young adults previously tested and reported (34) are indicated by closed circles (●). High affinity subjects had an average increase of 8.5% (range 7–10%) with a mean starting absolute heart rate of 103 (range 98–108). Normal subjects had an average increase of 33.8% (range 15–58%) with a mean starting absolute rate of 92 (range 76–105). This suggests a difference between groups in oxygen delivery during hypoxic response testing.

monoxide can itself lower PaO_2 (12) and can combine with carotid body cytochromes (13), introducing possible artifacts.

Similarly, experiments employing anemia are not entirely satisfactory. In addition to the difficulties inherent in the model (14), factors related to phlebotomy are known to influence chemoreceptor function and could affect the results obtained. These include sympathetic nervous activity (1), baroreceptor/chemoreceptor interactions (15), catecholamine effects (16), and possibly altered local blood flow (17).

A satisfactory model was more closely approximated in the study of goats with varying P_{50}s (14). Unfortunately, the animals were made anemic, thus adding to the objections above those of iatrogenic alterations of oxygen delivery such as decreased end-capillary PO_2 (18), altered cardiac output, and a possible shift towards anaerobic metabolism in low-P_{50} animals (19). Not surprisingly, conflicting results have also come from models employing polycythemia (20–23), which has complex effects on oxygen delivery (24).

In contrast, we feel that our experimental model introduces fewer potential artifacts than those used previously in the attempt to differentiate the effects of decrements in CaO_2 and PaO_2 on the carotid body. The use of control subjects from the same family minimizes the influence of familial variance of hypoxic drive (25). The use of unmanipulated subjects with differing P_{50}s in their steady state avoids many of the acutely induced problems of previously used models. On the other hand, a left-shift of the oxygen dissociation curve itself has complex, and as yet not fully defined, effects on oxygen delivery (26–28). For example, we were unable to directly measure such important parameters as arteriovenous oxygen gradients, end-capillary PO_2s, central nervous system acid-base status, actual cardiac output, or possible variations of local blood flows. Since these factors are as important as P_{50} and CaO_2 to tissue oxygen delivery, we acknowledge their potential but unknown influence on the peripheral and central chemoreceptors (and, hence, on ventilatory response) in these subjects. Nevertheless, the data presented herein show identity of ventilatory response to hypoxia in the subjects tested (Fig. 1A, Table I), regardless of their P_{50}s and despite marked differences in CaO_2 and apparent oxygen delivery (Figs. 2 and 3). If the carotid body were responsive to CaO_2 rather than PaO_2, there should have been a difference in response between normal and high oxygen affinity subjects.

A potential objection is the possibility of carotid body adaptation to a high oxygen affinity Hb. Since humans born at high altitude undergo progressive carotid body adaptation (29) with a concomitant blunting of ventilatory response to hypoxia (30), the possibility of analogous changes in our subjects cannot be ignored. However, the carotid body exposed to normal PaO_2 and adequate oxygen delivery (via compensatory erythrocytosis) (26) since conception is unlikely to have adapted in the manner stated. Moreover, chemoreceptor adaptation to high altitude takes years to develop (30, 31), and Byrne-Quinn et al. (32) have recently shown that children born at high altitude still have not acquired their altered ventilatory drive by the age of 10 yr (although there is also evidence contradicting this [33]). Thus, we feel that a carotid body adaptation (with blunting of ventilatory response) is possible but unlikely in our high affinity subjects.

We conclude that within the normal physiologic range, fluctuations of PaO_2 are the major determinant of hypoxic ventilatory response.

ACKNOWLEDGMENTS

We gratefully thank the subjects who participated in this study.

This investigation was supported by grants HL 19725 and HL 16833 from the National Institutes of Health, the Minnesota Lung Association, and Research Career Development Award HL 70356.

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