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Ventilatory response to high inspired carbon dioxide concentrations in anesthetized dogs

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Abstract

Background: The ventilation ($\dot{V}_I$) response to inspired CO_2 has been extensively studied, but rarely with concentrations >10%. **Aims**: These experiments were performed to determine whether $\dot{V}_I$ would increase correspondingly to higher concentrations and according to conventional chemoreceptor time delays. **Materials and Methods**: We exposed anesthetized dogs acutely, with and without vagotomy and electrical stimulation of the right vagus, to 20-100% CO_2-balance O_2.and to 0 and 10% O_2-balance N_2. **Results**: The $\dot{V}_I$ time delays decreased and response magnitude increased with increasing concentrations ($p<0.01$), but at higher concentrations the time delays were shorter than expected, i.e., 0.5 s to double $\dot{V}_I$ at 100% CO_2, with the response to 0% O_2 being ~3 s slower. Right vagotomy significantly reduced baseline breathing frequency (fR), increased tidal volume (VT) and increased the time delay by ~3 s. Bilateral vagotomy further reduced baseline fR and $\dot{V}_I$, and reduced the response to CO_2 and increased the time delay by ~12 s. Electro-stimulation of the peripheral right vagus while inspiring CO_2 caused a 13 s asystole and further reduced and delayed the $\dot{V}_I$ response, especially after bilateral vagotomy, shifting the mode from VT to fR. **Conclusions**: Results indicate that airway or lung receptors responded to the rapid increase in lung H^+ and that vagal afferents and unimpaired circulation seem necessary for the initial rapid response to high CO_2 concentrations by receptors upstream from the aortic bodies.

Keywords: Central chemoreceptors, lung chemoreceptors, nociceptors, peripheral chemoreceptors, vagotomy.

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Introduction

There are few studies that have investigated the relationship between the acute inspiration of very high CO_2 levels and the time delay and magnitude of the resulting change in ventilation ($\dot{V}_I$). At lower, more physiological, levels it is generally presumed that the magnitude of the response is directly related to the concentration; however the time delay is determined by a number of factors that need not be related to the concentration, such as: (a) lung to peripheral and central chemoreceptor circulation time, (b) nerve conduction velocity from receptor to brain to effecter organs and (c) baseline alveolar ventilation that determines the initial alveolar Pco_2 ($PAco_2$) and Po_2 (PAo_2).

Two factors that are potentially related to the CO_2 concentration are (a) the rate of rise of Pco_2 in the lung and receptor sites and (b) the associated stimulation of other receptors (nociceptors) in the larynx, airway, lungs or pulmonary veins by high CO_2. In order to determine whether the latter may be involved, these experiments were undertaken to measure the acute responses to inspired CO_2 levels from 20 to 100% in anesthetized dogs. Measurements were made before and after right and left vagotomy and superimposed stimulation of the right vagus nerve.

Materials and Methods

All experiments were performed on two female mongrel

dogs, weighing 8.4 kg each, on separate days, after which the animals were sacrificed. All procedures were in accordance with the Canadian Council of Animal Care guidelines. Dogs were anesthetized with 30 mg/kg Nembutal. The trachea was cannulated and the right and left vagus nerves isolated at the neck. A Y-tube was fitted to the tracheal cannula. Gas mixtures were prepared in a Douglas bag and valve, attached to one arm of the Y-connector placed in the tracheal cannula. Following a period of ~30 s, when baseline $\dot{V}_I$ was recorded, the valve from the bag was opened just prior to an inspiration, a time event marker indicated time zero for establishing the time of subsequent inspirations. Expiration took place through the other arm of the Y-connector that had a one-way valve that closed during inspiration. Recordings were continued until the tidal volume (VT) response to the test gas appeared maximal on the tracing.

Breath-by-breath chest expansion was obtained by an impedance pneumograph, and ventilation frequency (fR) and timing were obtained from subsequent measurements from polygraph recordings (1.0 cm/s) and time event markers. Heart rate (fH) was obtained by chest lead ECG. As the pneumograph recordings were uncalibrated, the height was expressed in units (U) to represent VT because the position of the impedance band may have moved and the contribution of the diaphragm to true VT may have varied between trials. Breath-by-breat $\dot{V}_I$ was calculated as U/min for each breath from the product of VT and fR calculated from the time between a given inspiration at the measured time and the previous one. $\dot{V}_I$ was then re-plotted on a time base relative to baseline $\dot{V}_I$ ($\dot{V}_{I/B}$) and averaged at specific times for the same conditions (up to six) at 0.5, 1.0 and 2.0 s intervals. Then average time delays from repeated trials with the various test gases were compared from the time of the first inspiration to where $\dot{V}_I$ was doubled ($2\dot{V}_{I/B}$) and quadrupled ($4\dot{V}_{I/B}$) from baseline $\dot{V}_I$. Time delays from time zero to where interpolated $\dot{V}_I$ exceeded 3 SD of baseline $\dot{V}_I$ were also noted as "response times."

All CO_2 mixtures were given in alternating order from low to high CO_2, (20, 40, 70 and 100%), with balance O_2 (80, 60, 30 and 0%, respectively). Hypoxic mixtures, 10% O_2-90% N_2 and 0% O_2-100% N_2, and air controls were interspersed randomly with the CO_2 trials. After these trials with both vagi intact, the 100% CO_2 and 0% O_2-100% N_2 trials were repeated with the right vagus and then both vagi cut. In addition the latter were repeated with the peripheral (efferent) end of the right vagus stimulated (60 Hz, 10 V, 5 ms) with a square wave generator at the same time that the gas was inspired to induce asystole to curtail the circulation. The baseline fH averaged 125/min after one or both vagi were cut before stimulation. Stimulation of the cut right vagus, with and without the left vagus cut, resulted in a 13 s asystole (range: 5 to 17 s), with vagal escape occurring over the next 10 s and fH then stabilizing at ~44/min during stimulation.

The time course of $PAco_2$ and PAo_2following inspiration of the test gas was estimated breath-by-breath from a) the mixing of measured VT and functional residual capacity (FRC) with the bag O_2 and CO_2 concentrations, assuming baseline $PAco_2$ = 35 mmHg and $PAco_2$= 99 mmHg and a baseline VT of 120 ml and FRC of 600 ml, as measured in dogs of similar weight by Muggenburg et al. [1] and b) an O_2 consumption of 5 ml/min/kg and baseline respiratory exchange rate of 0.80. The change in pH value (ΔpH) corresponding to changes in $PAco_2$ was calculated from the Henderson-Hasselbalch equation, assuming instantaneous equilibration between arterial Pco_2 and $PAco_2$, a pK of 6.1, a fixed bicarbonate (HCO_3^-) concentration of 24 mmol/L and no CO_2 storage in lung tissue; the latter would tend to buffer changes in $PAco_2$ [2].

Results

The average $\dot{V}_{I/B}$ responses to the four CO_2 concentrations, two hypoxic mixtures and air controls are depicted in Figure 1, with values in Table 1. The response time and time delay for the four CO_2 levels was inversely related to concentration and the magnitude was directly related; the inverse relationship between the highest three concentrations and time delays to $2\dot{V}_{I/B}$ and $2\dot{V}_{I/B}$ was linear. The responses to the two levels of hypoxia were similarly related to reduced O_2, but attenuated and slower than those for CO_2. For 100% CO_2 the response time was 0.3 s, with time delays of 0.5 s and 2.0 s at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$, respectively; the rise above baseline occurred on the first inspiration, with a greater VT (124%) and fR (8%) than baseline.

Figure 2 shows the $\dot{V}_{I/B}$ responses to the four CO_2 levels, along with the estimated $PAco_2$ at each inspiration. The 100% CO_2 trial (Fig. 2D) also shows the rapid PAo_2 decline with zero inspired O_2. The values for the instantaneous change/time of $PAco_2$ and $\dot{V}_{I/B}$ are shown at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$, assuming no time delay between $PAco_2$ and $\dot{V}_{I/B}$. The clear pattern is that $PAco_2$/s markedly increased with inspired CO_2 level as the time delay decreased, whereas $\Delta\dot{V}_{I/B}$/s was not markedly affected. $\dot{V}_{I/B}$ was greater at equivalent times as CO_2 concentration increased mainly because of the shorter time delays. The average of the individual time delays to $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ were significantly shorter for the 70 and 100% trials than for the 20 and 40% trials (1.8 vs. 23.5 and 3.4 vs. 32.8 s, respectively), with response times of 0.3 and 13.4 s ($p<0.01$ for all).

The percentage changes in fR and VT and estimated $PAco_2$, PAo_2 and ΔpH values at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ for all trials are included in Table 1. With vagi intact most of the $\dot{V}_I$ increase to $2\dot{V}_{I/B}$ for all CO_2 levels and 0% and 10% O_2 were due to increased VT, with an increasing, but still negligible contribution by fR at $4\dot{V}_{I/B}$. PAo_2 was ~70 mmHg when $2\dot{V}_{I/B}$ was reached for the 10% and 0% O_2 trials, but the time delay at 0% O_2 was 10 s less than at 10%. A comparison of baseline ventilatory

components before and after vagotomy shown in Table 1 shows a significant reduction in baseline fR, an increase in VT and no change in $\dot{V}_I$ after cutting the right vagus. Bilateral vagotomy further reduced fR, resulting in a significant reduction in $\dot{V}_I$ compared to right vagotomy alone.

The effects of right and bilateral vagotomy and superimposed right vagus stimulation on the response to 100% CO_2 and 0% O_2 are summarized in Figure 3. Stimulation of the cut right vagus by itself caused a small increase in $\dot{V}_{I/B}$ (Figs. 3B and 3C), mainly resulting from a greater fR, with the left vagus intact or cut (Table 1). Inspiring 0% O_2 after bilateral vagotomy increased the time delays to $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ by some 36 s (Fig. 3A), with the increased $\dot{V}_{I/B}$ resulting predominantly from increasing fR, whereas VT was the main contributor in the intact trials. Inspiration of 100% CO_2 with the right vagus cut (Fig. 3B) resulted in a vigorous response that was delayed about 4 s compared to that with the vagus intact, with VT still the main contributor. When the peripheral end of the right vagus was stimulated as CO_2 was inspired, the vigorous response was delayed an additional 5 s, with fR now the main contributor to the $\dot{V}_{I/B}$ increase. The effect of bilateral vagotomy on the response to CO_2 was qualitatively similar, but magnified (Fig. 3C). The time delay to $2\dot{V}_{I/B}$ was extended an additional 2 s after both vagi were cut, with $\dot{V}_{I/B}$ reaching a plateau at ~12 s. The relatively greater contribution of VT to the increase to $2\dot{V}_{I/B}$ remained about the same as with intact vagi, similar to hypoxia (Fig. 3A). When CO_2 was given during right vagal stimulation with both vagi cut the response was greatly attenuated and the time delay to $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ increased by an average of 15 s, with the fR contribution increasing compared with no stimulation.

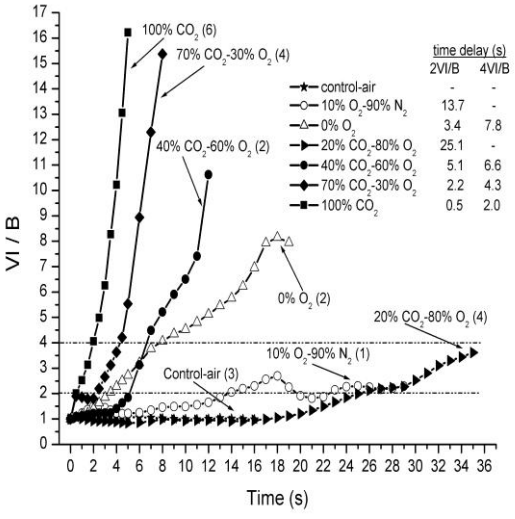

Fig. 1 Average $\dot{V}_{I/B}$ responses to seven conditions. Numbers in parentheses indicate number of trials for each condition. Time delays at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ are indicated as in Table 1.

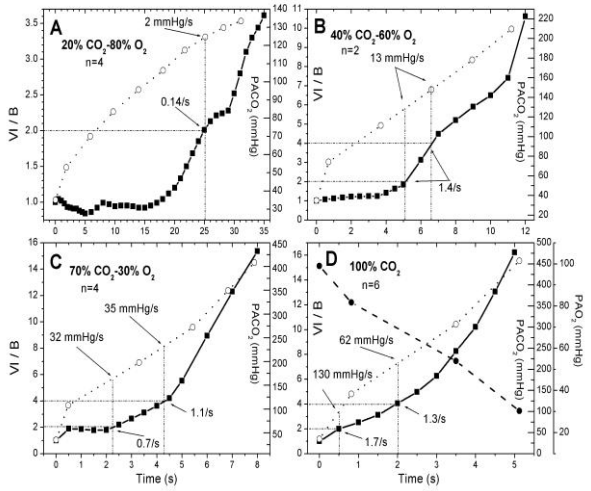

Fig. 2 Average $\dot{V}_{I/B}$ responses for four inspired CO_2 concentrations. Open circles indicate estimated $PAco_2$ for each breath. PAo_2 at 100% CO_2 is indicated by solid circles in panel D. Instantaneous values/time for $PAco_2$ and $\dot{V}_{I/B}$ are indicated at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$.

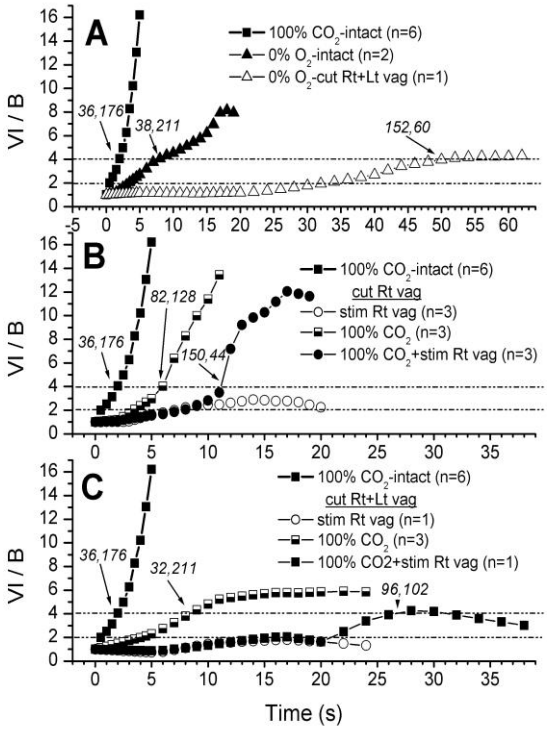

Fig. 3 Mean $\dot{V}_{I/B}$ responses to 100% CO_2 and 0%-100% N_2 before and after bilateral vagotomy (panel A). Panel B shows mean responses to 100% CO_2 before vagotomy, after Rt vagotomy while electrically stimulating the right (Rt) vagus and stimulation alone. Panel C indicates mean responses to 100% CO_2 before vagotomy, after bilateral vagotomy while stimulating the right vagus and stimulation alone. Numbers in italics indicate percentage change in fR and VT above baseline at $4\dot{V}_{I/B}$.

Table 1 Experimental conditions and averaged measurements for 14 trials in anesthetized dogs.

Experimental condition	n	Baseline $\dot{V}_I$ U x min^{-1}	Baseline fR min^{-1}	Baseline VT U	Baseline Res. time s	$\dot{V}_I/B$	Time s	ΔfR %	ΔVT %	PA_{O_2} mmHg	PA_{CO_2} mmHg	ΔpH
Control	3	28.3	15.8	1.79	- (-)	1.17	2.0	1	16	104	30	0.07
						4.0	-	-	-	-	-	-
10% O_2-90% N_2	1	34.1	26.0	1.31	1.3 (-)	2.0	13.7	15	74	66	13	0.43
						4.0	-	-	-	-	-	-
0% O_2-100% N_2	2	11.4	13.1	0.87	3.3 (2.6)	2.0	3.4	4	103	73	30	0.07
						4.0	7.8	38	211	45	23	0.18
0% O_2-100% N_2 (cut Rt+Lt vag)	1	11.8	6.3	1.88	24.3 (-)	2.0	32.8	55	29	18	32	0.04
						4.0	50.4	152	60	0	21	0.22
20% CO_2-80% O_2	4	18.0	19.4	0.93	18.3 (7.0)	2.0	25.1	-11	125	441	125	-0.55
						4.0	-	-	-	-	-	-
40% CO_2-60% O_2	2	16.6	26.0	0.64	3.7 (0.1)	2.0	5.1	-4	94	213	129	-0.57
						4.0	6.6	-3	310	235	148	-0.63
70% CO_2-30% O_2	4	21.0	22.8	0.92	0.3 (0.2)	2.0	2.2	6	90	127	163	-0.67
						4.0	4.3	11	263	141	233	-0.82
100% CO_2	6	19.0	15.3	1.24	0.3 (0.1)	2.0	0.5	5	91	88	100	-0.46
						4.0	2.0	36	176	69	215	-0.79
average with vagi intact	22	20.9 (1.4)	18.7 (1.8)	1.12 (0.10)								
stim cut Rt vag	3	15.3	9.3	1.64	6.3 (1.8)	2.0	7.1	51	18	104	31	0.05
						4.0	-	-	-	-	-	-
100% CO_2 (Rt vag cut)	3	24.6	10.1	2.44	2.1 (0.1)	2.0	3.4	28	47	74	176	-0.70
						4.0	6.0	82	128	61	248	-0.85
100% CO_2 + stim cut Rt vag	3	20.6	10.9	1.89	4.2 (1.7)	2.0	7.7	76	11	53	297	-0.93
						4.0	11.1	150	44	35	403	-1.06
average with cut Rt vagus	9	20.1 (3.6)	10.1 (0.6)*	1.99 (0.23)*								
stim cut Rt vag, Lt vag cut	1	12.4	6.9	1.80	9.8 (-)	2.0	17.1	173	-33	105	30	0.07
						4.0	-	-	-	-	-	-
100% CO_2 (cut Rt + Lt vag)	3	7.6	6.6	1.15	2.5 (1.0)	2.0	4.1	-11	136	82	120	-0.54
						4.0	8.4	32	211	59	249	-0.85
100% CO_2 + stim cut Rt vag, Lt vag cut	1	12.1	7.1	1.70	11.3 (-)	2.0	15.7	160	-24	45	314	-0.95
						4.0	26.5	96	102	20	451	-1.11
average with both vagi cut	6	9.8 (1.2)*#	6.7 (0.1)*#	1.47 (0.17)								

$\dot{V}_I$: inspired ventilation; fR: breathing frequency; VT: tidal volume; Res. time: response time for interpolated $\dot{V}_I$ to exceed baseline mean +3 SD; $\dot{V}_{I/B}$: inspired ventilation divided by baseline ventilation; Time: time from onset of first inspiration to $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ from average curve; ΔfR and ΔVT: percentage change in fR and VT from baseline to $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$; PAo_2 and $PAco_2$: estimated at $2\dot{V}_{I/B}$ and $4\dot{V}_{I/B}$ assuming baseline values of 99 and 35 mmHg, respectively; ΔpH: change estimated from PA_{CO2} change from baseline (35 mmHg) assuming fixed HCO_3^-; Parentheses: s.e.m.; *: value significantly ($p<0.05$) different from that with vagi intact; #: value significantly different ($p<0.05$) from value with Rt vagotomy

Discussion

These experiments strongly suggest that ventilation increases and the time delay decreases as the inspired CO_2 level approaches 100%. At levels ≥70% the time delay is shorter than reported for aortic arch and carotid body chemoreceptor response times from previous and subsequent studies. Vagotomy delayed the response to 100% CO_2 and restricting the circulation delayed it further.

That our limited experimental set-up was reasonable is partly supported by the following: (a) the changes in fR and VT with vagotomy during baseline (Table 1) agree closely with those reported in anesthetized dogs by Anrep and Samaan [3], who concluded that the slowing of respiration was due to denervation of the lungs and not the peripheral chemoreceptors, (b) the $\dot{V}_{I/B}$ response to hypoxia (Fig. 1 and Table 1) was not far removed from the 10 s time delay reported in humans and dogs and occurred at estimated PAo_2 values close to those reported for steady state breathing [4], (c) the $\dot{V}_{I/B}$ response leveled off with 100% CO_2 after vagotomy (Fig. 3C), as reported in dogs [5] and (d) the response was greatest and time delay shortest with 100% CO_2 when PAo_2 fell most rapidly (Fig. 2D), demonstrating the well-known enhanced ventilatory sensitivity to CO_2 when combined with hypoxia [6].

Studies of ventilatory responses to CO_2 and hypoxia in humans and mammals have typically utilized inspired concentrations of <10% CO_2 (inspired Pco_2<71 mmHg at sea level) and >10% O_2. Ventilatory studies using non-physiological concentrations >20% CO_2 have rarely been reported; when breathing concentrations >35% for some minutes it is an effective anesthetic in dogs [7]. In humans, repeated applications of 12 inspirations of a 30% CO_2-70% O_2 gas mixture were utilized by Meduna [8] some 6 decades ago to treat psychoneuroses and anxiety disorders with some success. The reaction to a mixture of 35% CO_2-65% O_2 has also been used as a trait marker for panic disorders [9]. Barcroft and Margaria [10] compared the ventilatory effect of CO_2 inhalation and exercise on themselves and stated, "The breathing of 7.5% of CO_2 for 20 minutes produces a shock from which the system does not wholly escape for some hours or perhaps even a longer time." They also measured the change in fR with the inspiration of 64% CO_2 in anesthetized cats [11] and noted that the increase was inversely related to baseline fR and that bilateral vagotomy resulted in an erratic response. Their recordings suggest a time delay of 4 to 5 s between first inspiration and ventilation increase. Dejours stated, "The existence of lung air chemoreceptors acting reflexly on the ventilatory regimen is generally not admitted," because, "These results have been observed only as a result of enormous and quite unphysiological shifts of Pco_2," and, "The hyperventilation resulting from breathing CO_2-rich mixtures does not occur before a lag of many seconds" [12]. On the other hand, Pi-suňer, in summarizing extensive chemoreceptor research prior to the early1940s [13], took exception to the statement by Cordier and Heymans [14] that, "-authors have administered by inhalation air with concentrations of CO_2 which pass beyond physiological limits and even beyond the pathological". Pi-suňer concluded from numerous experiments, "In addition to the well known action on the respiratory centers, there is exerted a parallel or perhaps previous peripheral influence due to the excitation of end-organs which are sensitive to stimuli of chemical nature by the CO_2 contained in the inspired air" [13]. Our results support the latter in the continuing controversy regarding lung chemoreceptors, the same as many early studies based on the ventilation response to higher concentrations.

The aortic arch and carotid body (peripheral) and central medullary chemoreceptors all respond to CO_2 and hydrogen ion concentration (H+) to increase ventilation; the relative contributions of these responses to this rise following the stimuli of lung or blood CO_2/H+ have been studied extensively and remain controversial, especially with variations in baseline arterial blood P_{O2} (12, 15, 16]. Recent studies with isolated carotid sinus perfusion show that the central chemoreflex can respond to an increase in PA_{CO2} in unanesthetized dogs in 6 s, but take 11 s longer when separated from peripheral receptors [17]; this demonstrates that the gain of the central receptors is critically dependent on the peripheral ones [18]. It is often not clear whether reported time delays pertain to central and/or peripheral receptors, but the latter should respond first to the CO_2/H+ signal.

Time delays result primarily from the lung-to-chemosensor circulation time. Our average time delay from first inspiration to $2\dot{V}_{I/B}$ was inversely related to CO_2 concentration, ranging from 25.1 to 0.5 s, for 20 and 100%, respectively. The lung to brain time delay from an increase in $PAco_2$ to affect pH at the medulla oblongata in unanesthetized cats has been reported to be 5 to 7 s [19]. In humans the peripheral response to inspiring hypoxic gas has been measured at 5 s, from lung-to ear circulation time by oximetry [20]. McClean et al. [21] measured a 10 s delay to peak ventilation after a single breath of 13% CO_2-balance air in healthy humans and suggested this as a test for peripheral chemoreceptor function in patients. The time delay from infusion of CO_2-equilibated blood into the aortic arch to increase ventilation was found to be 6.6 s in unanesthetized dogs by Sylvester et al. [22], who

concluded that the circulation time from aortic arch to aortic body, carotid body and the medulla to be 1, 3-4 and 5-6 s, respectively. Definitive time delay experiments in unanesthetized dogs were reported by Gonzalez et al. [23]. They measured the time from injection of cold $NaHCO_3$ to the increase in ventilation to be 2.0 and 6.9 s, when injected into the aortic arch and superior vena cava, respectively. The corresponding times for arrival of the blood to these sites were 1.9 and 3.7 s. The time from the $PAco_2$ rise in the lung, induced by the $NaHCO_3$, to arrival at the carotid body was about 1 s, implying a lung stimulus to ventilation response time of ~3 s.

An important consideration is that a rapid response in fR and/or VT during the first inspirate will increase the rate of rise of $PAco_2$ to raise the alveolar/arterial blood stimulus level for the downstream arterial chemoreceptors (Fig. 2). Carbonic anhydrase, present in the interstitial lung tissue, would be expected to rapidly convert CO_2 to H+ in the pulmonary capillaries and then stimulate the downstream chemoreceptors [24, 25]. At 100% CO_2, with concurrent hypoxia, the fall in pH would be partially attenuated due to the Haldane effect [26]. Assuming that effect is negligible and with instantaneous equilibration of lung-blood $PAco_2$ and pH, the VT and fR measurements, and interpolating $PAco_2$ for the times courses in Fig. 2 at 2 s, the estimated lung tissue pH decreased 0.19, 0.41, 0.65 and 0.79 as inspired CO_2 fractions increased, respectively. With the right vagus cut the pH fell 0.59 with 100% CO_2 and to 0.34 with both cut. This is about half the increase in H+ compared to that with the vagi intact. Bartoli et al. [27] emphasized the difficulty of separating the chemoreceptors involved in responding to inhaled CO_2 vs. hypercapnic blood. They noted a vagally mediated response to inspired CO_2 on the first breath that was absent after vagotomy, similar to our results. Our responses to CO_2 in Fig. 2 at 20 and 40% in intact dogs suggest stimulation of peripheral and central chemoreceptors without an initial rapid response, as the time delays are within those reported. However, at 70 and 100% the response is faster than can be explained by those.

Our results imply that there is a third sensing site, upstream from the aortic bodies in or near the lung that is dependent on vagal afferents. We speculate that nociceptors are involved. Laryngeal CO_2 receptors have been noted in anesthetized dogs [28] and when these myelinated and unmylenated fibers in the vagus were blocked the reflex was decreased [29]. These sensing regions are located in the trachea and larger bronchi, where they are more chemosensitive, and can stimulate ventilation. They probably add to the response of the unmylenated C-fibers in contributing to the total reflex response [30]. There is also evidence that the J-receptors [31, 32] and vagal bronchopulmonary C-fiber sensory nerves are also involved in the rapid ventilatory responses to lung irritants and may contribute to dyspnea in patients with COPD [33, 34]. Furthermore, these C-fibers have been shown to respond rapidly in dose-related fashion to H+ induced by injections of lactic acid in anesthetized rats [35, 36]. An increase in $PAco_2$, acting via H+, has been shown to augment the responses of the C-fibers to chemical stimulants [37].

The estimated pH changes shown in Table 1 exceed those reported to be effective in C-fiber stimulation in anesthetized rats. The high CO_2 or H+ acting as a direct irritant, could explain our results with 70 and 100% CO_2 (Fig. 3B). Both the near instantaneous C-fiber response and part of the peripheral reflex are abolished by vagotomy, accounting for the delayed response, which then results only from central chemoreceptors. The response by the latter is further reduced when the peripheral receptor potentiation is partially removed by cutting both vagi (Fig. 3C) and further delayed by slowing the circulation by stimulating the efferent right vagus.

Conclusion

Our indirect evidence for fast-acting chemoreceptors in the broncho-tracheal region to high CO_2/H+ concentrations can be criticized for having too few animals and lack of ancillary respiratory measurements. Certainly a shift in baseline acid-base status because of repeated trials with CO_2 would have an effect on the response curves. However, the time delays were carefully measured and suggest that more experiments are required to determine the contribution of airway and lung area chemoreception to the control of ventilation when alveolar Pco_2 is rapidly altered.

Acknowledgements

These experiments came about as a result of skepticism expressed in 1978 by Professor G. Bonar Sutherland, Department of Physiology and Pharmacology, University of Saskatchewan, who stated; “I’m not satisfied that current peripheral/central chemoreflex hypotheses completely explain the rapid ventilation response to CO_2.”

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