Carbon dioxide added late in inspiration reduces ventilation-perfusion heterogeneity without causing respiratory acidosis

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Brogan, Thomas V., H. Thomas Robertson, Wayne J. E. Lamm, Jennifer E. Souders, and Erik R. Swenson. Carbon dioxide added late in inspiration reduces ventilation-perfusion heterogeneity without causing respiratory acidosis. J Appl Physiol 96: 1894–1898, 2004. First published December 5, 2003; 10.1152/japplphysiol.00160.2003.—We have shown previously that inspired CO₂ (3–5%) improves ventilation-perfusion (V˙ A/Q˙) matching but with the consequence of mild arterial hypercapnia and respiratory acidosis. We hypothesized that adding CO₂ only late in inspiration to limit its effects to the conducting airways would enhance V˙ A/Q˙ matching and improve oxygenation without arterial hypercapnia. CO₂ was added in the latter half of inspiration in a volume aimed to reach a concentration of 5% in the conducting airways throughout the respiratory cycle. Ten mixed-breed dogs were anesthetized and, in a randomized order, ventilated with room air, 5% CO₂ throughout inspiration, and CO₂ added only to the latter half of inspiration. The multiple inert-gas elimination technique was used to assess V˙ A/Q˙ heterogeneity. Late-inspired CO₂ produced only very small changes in arterial pH (7.38 vs. 7.40) and arterial CO₂ (40.6 vs. 39.4 Torr). Compared with baseline, late-inspired CO₂ significantly improved arterial oxygenation (97.5 vs. 94.2 Torr), decreased the alveolar-arterial P O₂ difference (10.4 vs. 15.7 Torr) and decreased the multiple inert-gas elimination technique-derived arterial-alveolar inert gas area difference, 0.36 vs. 0.22). In conclusion, we have established that the majority of the improvement in gas exchange efficiency with inspired CO₂ can be achieved by limiting its application to the conducting airways and does not require systemic acidosis.

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LOW CONCENTRATIONS (3–5%) of CO₂ added during inspiration improve gas exchange and arterial oxygenation in normal lungs (8, 12). Our laboratory used the multiple inert-gas elimination technique (MIGET) to demonstrate that inspired CO₂ improves arterial oxygenation by reducing ventilation-perfusion (V˙ A/Q˙) heterogeneity (22). In further work, our group found that the influence of CO₂ on V˙ A/Q˙ matching was associated with decreased regional pulmonary blood flow heterogeneity, as assessed by injected fluorescent microspheres (4).

Numerous studies in whole lungs and isolated airways and blood vessels reveal that CO₂ and acidosis have several effects that have the potential to improve V˙ A/Q˙ matching (for review, see Ref. 23). They relax airway smooth muscle (3, 6, 7, 16, 20, 21, 27), whereas hypocapnic hyperventilation causes bronchoconstriction (12, 27). CO₂ also increases collateral ventilation in many species (24) and enhances the surface tension-lowering properties of alveolar surfactant to increase lung compli-

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METHODS

Animal instrumentation and support. The Animal Care Committee of the University of Washington School of Medicine, Seattle, Washington, approved all aspects of procurement, care, nutrition, experimental protocol, anesthetic use, and euthanasia in these experiments. Studies were performed on 10 healthy mixed breed dogs (weight range: 20–28 kg) in the supine position under barbiturate anesthesia (20–30 mg/kg iv sodium pentothal induction with supplemental doses, 1–2 mg/kg as needed every 30–60 min). The animals underwent intubation with auffed endotracheal tube. Femoral arterial and venous catheters were inserted, and a jugular 7-Fr thermodilution catheter was advanced into the pulmonary artery. Temperature was
monitored by the pulmonary artery catheter. Ventilation was administered by a piston pump ventilator at a tidal volume of 12–13 ml/kg and a rate of 14–16 breaths per minute. Every 5 min, a single 30 ml/kg breath was provided to prevent atelectasis. Once an acceptable rate of ventilation was determined by arterial blood-gas analysis [arterial pH of 7.39–7.45 and arterial PCO2 (Paco2) of 35–40 Torr], no further changes in ventilator settings were made. After the experiment, the dogs were killed by an overdose of thiopental sodium.

**Hemodynamics and respiratory gas exchange measurements.** Pulmonary and systemic arterial pressures, airway pressures, and mixed expired CO2 and O2 fractions (FeCO2 and FeO2, respectively) were continuously recorded on an eight-channel recorder (Hewlett-Packard, Palo Alto, CA). At specified intervals, pulmonary artery occlusion pressure, thermodilution cardiac outputs, and mixed expired FeCO2 and FeO2 (sampled from a 3-liter mixing box) were determined. FeO2 and FeCO2 in expired gas were measured by a mass spectrometer (Perkin-Elmer medical gas analyzer MGA-1100, Norwalk, CT). Blood pH and partial pressures of O2 and CO2 in arterial and mixed venous blood were measured on a blood-gas analyzer (Radiometer BMS-3, Radiometer America, Westlake, OH) maintained at 37°C and corrected to the pulmonary artery temperature. O2 consumption (Vo2) and CO2 production (Vco2) were calculated by analysis of expired gases using appropriate temperature, pressure, and water content corrections.

Respiratory gas exchange was assessed by analysis of arterial and mixed venous blood gases. In calculating (A-a)PO2, we used the complete alveolar gas equation that incorporates inspired CO2 fraction (FI CO2) (25).

The addition of CO2 late in inspiration complicates the analysis of measured mixed expired CO2 and O2 for the calculations of VO2 and VCO2. Because we know the tidal volume, the frequency, and the amount of 100% CO2 added into the last half of inspiration, it is possible to calculate the mean weighted corrected inspired O2 fraction (Fio2) and FeCO2, for purposes of calculating the CO2 and VCO2 under the conditions of adding a gas into only a portion of the inspirate

\[
\text{FeCO2\text{(corrected)}} = \frac{(V_{\text{add gas}} \times F_{\text{CO2\text{ added gas}}} + (V_i \times F_{\text{CO2}})}{(V_{\text{add gas}} + V_i)}
\]

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\]

where \(V_{\text{add gas}}\) is the total volume of gas in the injected CO2, FeCO2 (0.000) and FeO2 (0.209) are the inspired fractions of CO2 and O2 in the breath delivered by the ventilator, and FC02 added gas (1.000) and FO2 added gas (0.000) are the fractions of CO2 and O2 in the injected gas volume. On average these yielded a corrected FeCO2 of 0.023 and a corrected FeO2 of 0.206. However, in calculating alveolar PO2 (PAO2) and the (A-a)PO2 from the alveolar gas equation, we assumed that none of the added CO2 reached the alveolar space. Consequently we corrected the measured values for mixed expired O2 and CO2 with the following equations

\[
\text{FeCO2\text{(corrected)}} = \text{FeCO2} - \frac{(V_{\text{add gas}} \times F_{\text{CO2\text{ added gas}}} + (V_i \times F_{\text{CO2}})}{(V_{\text{add gas}} + V_i)}
\]

\[
\text{FeO2\text{(corrected)}} = \text{FeO2\text{(measured)}} \times \frac{(V_{\text{add gas}} + V_i) + (V_{\text{add gas}} \times F_{\text{O2\text{ added gas}}})}{V_i}
\]

**Inert gas exchange measurements.** VA/Q relationships were determined by MIGET (28, 29) using a constant infusion of a dilute solution of six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone) dissolved in 5% dextrose solution as described by Wagner and coworkers (28, 29). The gas extraction method of Wagner et al. (28) was used to determine inert gas tensions and solubilities in blood samples. Inert gas indexes were calculated from the 50-compartment model of Wagner et al. (29). VA/Q heterogeneity was also assessed by the arterial-alveolar difference area (a-A)D area, derived directly from the retention and excretion data (10). All inert gas data are the average of duplicate measurements.

**Experimental protocols.** Each dog underwent the same protocol, serving as its own control. After stabilization and a 20-min period of ventilation with room air, baseline hemodynamic (cardiac output, heart rate, systemic and pulmonary artery pressures), ventilation and respiratory gas exchange (arterial and mixed venous blood gases, minute ventilation, airway pressures, and VO2 and VCO2), and inert gas exchange measurements (arterial and mixed venous blood gases, and mixed expired gas) were taken. After these measurements, the animal was ventilated with 5% CO2 mixed into room air (as measured in the inspiratory gas by mass spectrometry), leading to an inspired O2 of 19.9 ± 0.1%. After 20 min, all measurements were repeated, and then the animal was returned to room air ventilation. Next, the dogs received room air ventilation with a small quantity (4–15 ml) of CO2 added to the last half of inspiration. This was done by smooth hand injection of the CO2 over the full second half of the inspiratory phase. The order of the different CO2 exposures was randomly determined by a coin toss.

**Statistical analysis.** All data are presented as means ± SD and were analyzed by repeated-measures ANOVA followed by Scheffe’s and Bonferroni/Dunn post hoc tests corrected for multiple comparisons of similar data sets and for comparisons over time. Differences between individual experimental points were analyzed by Wilcoxon’s signed-rank test.

**RESULTS**

Minute ventilation was fixed at 6.0 ± 1.5 l/min. The concentration of CO2 during late CO2 was 2.4 ± 0.8% of total tidal volume and 4.9 ± 0.06% during continuous inspired CO2. The FO2 during continuous inspired CO2 was 0.199 ± 0.006.

Hemodynamic and ventilatory effects of room air, 5% CO2 and late-inspired CO2 are listed in Table 1. Mean systemic blood pressure was unchanged by either CO2 treatment, but mean pulmonary artery pressure increased significantly with 5% CO2. Cardiac output increased with inspired 5% CO2, approaching statistical significance (P = 0.06). Late-inspired CO2 had no significant hemodynamic effects. Pulmonary artery occlusion pressure, peak airway pressure, hematocrit, and temperature did not significantly change in either experimental condition. For seven animals in which we collected expired gas for calculation of VO2 and VCO2, there were no differences in VO2 (room air, 0.16 l/min; late CO2, 0.16 l/min; 5% CO2, 0.15 l/min). For VCO2, there was no difference between room air and late CO2.

<table>
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<th>Table 1. Hemodynamic and ventilatory measurements</th>
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<td>Room Air</td>
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Values are means ± SD; n = 10 dogs. SBP, mean systemic blood pressure; Ppa, mean pulmonary artery pressure; Q, cardiac output; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance, Paw, peak airway pressure. *P < 0.05 compared with baseline; †P < 0.01 compared with baseline.
late CO₂ (0.15 vs. 0.16 l/min), but a small fall with 5% CO₂ to
0.12 l/min (P < 0.05).

Table 2 provides respiratory gas exchange data. Both late-
inspired CO₂ and 5% CO₂ produced a significant improvement
in P a O₂. A decrease in pH was significant in both experimental
conditions, but late-inspired CO₂ only decreased pH from 7.40
to 7.38, a clinically insignificant change. Late-inspired CO₂
also had no significant effect on P a CO₂, whereas continuous
inspired 5% CO₂ significantly increased P a CO₂. Late-inspired
CO₂ improved mixed venous PO₂ by 9.6 Torr, whereas con-
tinuous inspired 5% CO₂ increased mixed venous PO₂ by 9.6
Torr. There were no differences in P a O₂ with either late-
inspired 5% CO₂ or 5% CO₂. However, given the fact that the F i O₂
with 5% CO₂ was 0.199, the P a O₂ of 113 Torr underestimates
the (A-a)PO₂, and alveolar O₂ partial pressures, respectively; Pa CO₂, arterial CO₂ partial
pressures; pH₂, arterial pH. *P < 0.05 compared with baseline; †P < 0.01
compared with baseline.

The major finding of this study is that when CO₂ is added
during the latter half of inspiration, limiting it to the conducting
airways, there is improved arterial oxygenation, a reduction in
the log standard deviations of the perfusion distribution and
ventilation distribution approaching significance with both
(P = 0.08 and 0.07, respectively). Shunt fraction and inert gas
dead space were not affected by either late-inspired CO₂ or
5% CO₂.

Table 4 provides the mean retention and excretion values for
the six inert gases in all three experimental conditions. For
each gas, except acetone, there were statistically significant
increases in excretion with 5% CO₂. Otherwise there were no
statistically significant differences in retention for either late
CO₂ or 5% CO₂. However, inspection of Table 4 shows that for
late CO₂ the mean excretion values for all the inert gases
except acetone were increased, suggesting a partial dose-
response effect intermediate to that of 5% CO₂.

Figure 1 plots the percentages of ventilation and perfusion
across seven discrete V a/Q ranges from shunt through dead
space for the three conditions. These data show that both late
CO₂ and 5% CO₂ cause a shift of ventilation out of high V a/Q
regions (V a/Q = 10–100) into regions of midrange V a/Q ratios (0.1–10).

**DISCUSSION**

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Critical of methods. Late CO$_2$ was added by manually injecting a small aliquot (4–15 ml) of 100% CO$_2$ gas to the latter half of inspiration by following a pneumograph tracing. Thus there likely were small variations in breath-to-breath delivery of the CO$_2$ with respect to its appearance during the inspiration. Nevertheless, we were successful in restricting the delivery of CO$_2$ to the conducting airways because we essentially had no uptake of the added CO$_2$. The 0.02 pH change and 1 Torr rise in P$_{aCO_2}$ were trivial compared with the 0.12 pH unit and 15 Torr P$_{aCO_2}$ change with 5% CO$_2$ throughout inspiration. The concentration of CO$_2$ during late CO$_2$ was 2.4% when calculated for the entire breath but would be 4.8% for the final half of inspiration and hence similar in concentration to the continuous CO$_2$.

We studied dogs that were healthy by all outward appearances, but the inert gas data showed a greater degree of V/A/Q heterogeneity than normal. Some of the dogs were studied in the fall when kennel cough is prevalent, and this may have contributed to some of the greater dispersion in our baseline V/A/Q heterogeneity. Nevertheless, the effectiveness of inhaled CO$_2$ was evident regardless of the baseline state of gas exchange.

Effects of CO$_2$ on gas exchange. The nearly equal improvements in V/A/Q matching observed with late-inspired CO$_2$ compared with continuous CO$_2$ establish that the majority of the effect of inspired CO$_2$ can be attributed to local effects in the lung. Addition of CO$_2$ in the latter half of inspiration exposes the conducting airways to a near-constant CO$_2$ tension throughout both phases of breathing without changing alveolar P$_{aCO_2}$. The high diffusibility of CO$_2$ leads to a lower extra- and intracellular pH within the airway epithelium and surrounding smooth muscle than during breathing of CO$_2$-free gas. Intracellular and extracellular acidoses directly relax bronchial smooth muscle (3, 6, 16, 20, 21, 27). The bronchodilating effects of CO$_2$ may not be equal throughout the lung owing to differences in local ventilation and V/A/Q ratio. Thus areas of low ventilation and V/A/Q ratio may be intrinsically more bronchoconstricted and therefore could be more responsive to the dilating effect of a rise in local CO$_2$. In this manner, ventilation may be redistributed out of highly ventilated areas into poorly ventilated regions, with the net result that the ratio falls in high V/A/Q regions and rises in low V/A/Q regions. This is consistent with the changes in ventilation to V/A/Q ratio shown in Fig. 1. We have recent and direct evidence for this pattern of regional ventilation redistribution in dogs ventilated with 5% CO$_2$ studied with aerosolized 1-μm fluorescent microspheres (5).

Although late-inspired CO$_2$ would be expected to have only airway effects, the distribution of regional perfusion may also be altered. Our data in dogs with fluorescent microspheres show that inspired CO$_2$ produces a more homogeneous distribution of regional perfusion (4). Transairway diffusion of CO$_2$ to the accompanying pulmonary arterioles with hypercapnic acidotic pulmonary vasoconstriction and/or CO$_2$-mediated augmentation of hypoxic pulmonary vasoconstriction offers an explanation for a late-inspired CO$_2$ effect on regional perfusion distribution despite that fact that inspired CO$_2$ only reaches the nonrespiratory bronchioles. Direct evidence for transairway gas exchange with accompanying pulmonary arterioles comes from human studies with H$_2$-sensitive platinum electrodes wedged into 2- to 3-mm pulmonary vessels (11, 19). The accompanying bronchi are sixth- to eighth-generation branches in the midportion of the conducting airway system (30). When subjects inhaled a single breath of H$_2$-rich gas, there was a within-breath response of the vascular electrode, in contrast to delayed signal consistent with alveolar H$_2$ uptake and return to the pulmonary artery via normal circulation when the electrode-tipped catheter was pulled back out of the wedged position (11, 19).

With CO$_2$ present in the entire breath, there is CO$_2$ uptake and systemic respiratory acidosis. Thus improvements in oxygenation and V/A/Q matching may not entirely result from local effects of CO$_2$ in the lung. Systemic hypercapnia can increase
Pao2 in two ways, independent of any change in V/AQ heterogeneity. First, the Bohr effect with systemic hypercapnic acidosis will lead to a higher PO2 in both arterial and venous blood, for the same degree of hemoglobin saturation and blood O2 content (26). Second, an elevated mixed venous PO2 from the Bohr effect and an increased venous O2 content arising from a slightly greater cardiac output but unchanged VO2 (Table 1) will lead to a higher Pao2 for any degree of fixed V/AQ mismatch (9). Last, systemic hypercapnia may improve V/AQ matching via neural reflexes involving airways and pulmonary vessels (23) arising from the peripheral and central chemoreceptors, as is true for peripheral chemoreceptor-mediated reduction of hypoxic pulmonary vasoconstriction (32).

In conclusion, our data establish that increases in CO2 limited to the conducting airways during inspiration improve gas exchange in the lungs of dogs because of a decrease in V/AQ heterogeneity. In normal lungs, an improvement in arterial oxygenation of only 4 Torr, and an equivalent drop in (A-a)PO2, may seem a small effect, but it must be appreciated that, in health, gas exchange efficiency is already quite good and may not be much improved on. However, CO2 addition into the latter half of inspiration in many states of lung dysfunction may yield more significant improvements when V/AQ mismatching is greater. Last, addition of CO2 into the latter half of inspiration offers a potential therapeutic strategy to enhance gas exchange and suppress local inflammatory events in lung injury when patients cannot tolerate further additional respiratory acidois with tidal volume reduction (lung-protective ventilation or permissive hypercapnia) or CO2 added uniformly into the inspired gas (15, 17).

GRANTS

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REFERENCES