Using Statistical Techniques to Predict Dynamic Arterial P_{CO_2} in Patients With COPD During Maximum Exercise

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BACKGROUND: P_{aCO_2} as measured during exercise in patients with COPD is poorly predicted (predicted P_{aCO_2}) from lung function testing and some noninvasive measurements, such as end-tidal P_{CO_2} (P_{ETCO_2}). OBJECTIVE: We performed a number of statistical techniques on P_{ETCO_2} and its interaction with other physiologic variables during exercise testing, in order to improve our ability to predict P_{aCO_2}. The estimated P_{aCO_2} as determined from these techniques may therefore be used to contrast the P_{ETCO_2} readings that are measured during an incremental exercise test on a breath-by-breath basis (ie, $P_{aCO_2} - P_{ETCO_2}$), and to identify exercise-induced hypercapnia. METHODS: Forty-seven men with COPD underwent both pulmonary function testing and incremental exercise testing until limited by symptoms. Arterial blood gases and exercise physiological measurements were performed during maximal exercise testing. The prediction equations for P_{aCO_2} were generated using regression techniques with the leave-one-out cross-validation technique. RESULTS: Forty-one patients were included in the final analysis after 6 patients were excluded due to inadequate data collection. The best prediction equation we found was: predicted $P_{aCO_2} = 23.71 + P_{ETCO_2} \times (0.9 - 0.01 \times D_{LCO} - 0.04 \times V_T) - 2.61 \times SVC - 0.04 \times MEP$, where D_{LCO} is diffusing capacity for carbon monoxide in mL/min/mm Hg, V_T is tidal volume in L, SVC is slow vital capacity in L, and MEP is maximum expiratory pressure in cm H_2O. The difference between the measured and predicted P_{aCO_2} at each time point was not statistically significant (all $P > .05$). The standard errors of the estimated P_{aCO_2} at each time point were 0.91–1.12 mm Hg. CONCLUSIONS: A validated mixed-model regression derived equation yields a predicted P_{aCO_2} trend during exercise that can be helpful when interpreting exercise testing to determine $P_{aCO_2} - P_{ETCO_2}$ and exercise-induced hypercapnia. *Key words: hypercapnia; capnography; bicycle ergometer; ventilatory limitation; mixed model; leave-one-out technique*. [Respir Care 2012;57(7):1106–1114. © 2012 Daedalus Enterprises]

Introduction

Arterial P_{CO_2} (P_{aCO_2}) is governed by integrated alterations in minute ventilation ($\dot{V}_E$), physiologic dead-space to tidal-volume ratio (V_D/V_T), and carbon dioxide output ($\dot{V}_{CO_2}$) (ie, Bohr equation). Exercise-induced hypercapnia (EIH) is a sign of inadequate ventilation that is due to a

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number of physiologic changes in a patient with COPD, including hyperinflation, reduced gas exchange capabilities (ventilation/perfusion mismatch), increased V_D/V_T, and more rarely the opening of a right-to-left shunt.[1,2] It is important to detect the development of EIH in this patient population so that we may appreciate its mechanisms and consider additional management strategies.

P_{aCO_2} is highly variable and is poorly predicted from resting lung function testing.[3,4] While there are noninvasive tools[2,5,6] to measure this parameter, there are many technical limitations[6,7] or conditions, such as anesthesia, mechanical ventilatory support,[8-10] old age,[11,12] or COPD,[13] that impact its measurement. The diagnosis of EIH or increased V_D/V_T is invasive and requires an arterial line. The multiple arterial blood gas measurements that may be drawn to determine the V_D/V_T are also costly.

The inaccuracies of estimating a predicted P_{aCO_2} can be improved by considering end-tidal P_{CO_2} (P_{ETCO_2}) plus V_T in normal adults[14] or FEV_1 plus V_T in patients with COPD.[3] Other factors, such as exertional hyperinflation, weakened inspiratory muscles, and deranged neuroregulatory control, may also have an impact on EIH.[1] Therefore we assumed that it would be too difficult to improve the accurate predicting of P_{aCO_2} by conducting any further physiological studies. We then hypothesized that by recruiting more physiological variables for statistical analysis our ability to predict P_{aCO_2} would be improved in adults with COPD.

The study was designed to identify variables for deriving equations that would more accurately estimate P_{aCO_2} trends in patients with COPD during maximum exercise testing. The clinicians can compare the P_{ETCO_2} trend of the popularly used 9-panel plot breath-by-breath[15] with the equation-derived estimated P_{aCO_2}. A clinician's ability to detect reduced alveolar ventilation and gas exchange capabilities in patients with COPD could be enhanced by this information.

QUICK LOOK

Current knowledge

P_{aCO_2} is difficult to predict from noninvasive measures in patients with chronic lung disease during exercise testing. Alterations in ventilation/perfusion complicate this prediction.

What this paper contributes to our knowledge

The best prediction equation for P_{aCO_2} was a mixed model regression technique that included P_{ETCO_2} slow vital capacity, maximum expiratory pressure, diffusing capacity for carbon monoxide, and tidal volume. The best way to ascertain exercise induced hypercapnia, the difference between P_{aCO_2} and end-tidal CO_2, or the ratio of dead space to tidal volume remains analysis of arterial blood.

Methods

Forty-seven patients, age 50–76 years, with COPD of varying severity, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[16] were enrolled to participate in this study. All subjects were clinically stable out-patients receiving a regular schedule of orally administrated or inhaled bronchodilators, with or without oral prednisolone of < 10 mg per day. Patients with substantial underlying arrhythmias, a history of malignancy, diabetes mellitus, cardiovascular or peripheral vascular disease, or locomotion problems were excluded from the study. The patients did not participate in any physical training protocol. However, regular activity was not limited. The exercise protocol and procedure, as well as the risks of maximal exercise testing, were explained. The institutional review board approved this study, and all subjects gave their consent to participate.

To derive equations for predicting P_{aCO_2} trends, we prospectively collected lung function and exercise data, utilizing multiple arterial blood gas analyses from patients with COPD, while they were at rest and while performing a ramp-pattern exercise testing protocol. Several steps of model screening were performed to select candidate equations. Both goodness-of-fit measures and cross-validation techniques were used to assess the model's validity. Because of the invasiveness of inserting an arterial line, the cost of multiple arterial blood gas analyses, and limited study subjects, a leave-one-out cross-validation was performed, instead of recruiting another large sample to validate the equation. (See the statistical analysis section.)

Pulmonary Function Testing

To select eligible subjects for this study we used spirometry to evaluate the severity of air-flow obstruction. For a detailed description of the lung function test performed, please refer to the study by Chuang et al.[17] The lung function test was performed before exercise testing and included maximally forced expired flow curves, lung volumes, maximum voluntary ventilation, and diffusing capacity for carbon monoxide (D_{LCO}) (6200 Autobox DL, SensorMedics, Yorba Linda, California). Maximum inspiratory pressure was measured at residual volume (RPM, Micro Medical, Rochester, Kent, United Kingdom). Maximum expiratory pressure was measured at total lung capacity. Maximum inspiratory pressure and maximum expiratory pressure were each performed 3 times with a one-minute recovery period between efforts. The best result was recorded for analysis.

Maximal Cardiopulmonary Exercise Test

Stable exercise gas exchange was initially obtained while the subject sat at rest on the cycle ergometer ($CardiO_2$, Medical Graphics, St Paul, Minnesota). Data were collected during a 2-min period of rest, followed by a 2-min period of unloaded cycling, followed by a ramp-pattern cycle ergometer exercise test to exhaustion. The work rate was increased at a rate of 5–20 watts per minute, according to the subject's individual fitness. The rate of increase was selected so the subject was able to complete the test within approximately 10 min.[18,19] Oxygen uptake ($\dot{V}_{O_2}$) (mL/min), CO_2 production ($\dot{V}_{CO_2}$) (mL/min), and $\dot{V}_E$ (L/min) were computed breath by breath, and the data were displayed every 15 seconds, using an on-line computer program. We designated the $\dot{V}_{O_2}$max as the peak or maximum $\dot{V}_{O_2}$ that the patient achieved. Twelve-lead electrocardiography, heart rate, and S_{pO_2} using a pulse oximeter (Ohmeda 3740, BOC Healthcare, Manchester, United Kingdom) were measured continuously.[20]

Blood Gas Measurement

A catheter was inserted into the brachial artery of the non-dominant arm, under local anesthesia. The indwelling catheter was then fixed in place and the forearm was splinted. For each subject, blood was sampled using heparinized syringes at rest, during unloaded cycling, during loaded cycling at one-minute intervals, and at peak exercise. The blood samples were drawn slowly over an approximately 15 second interval, at the end of each stage of exercise, to include measurements from several breaths to help rid the data of breath-by-breath variability.[21] The samples were immediately placed on ice and then analyzed for pH, P_{aO_2}, and P_{aCO_2}, using a gas analyzer (model 278, Ciba-Corning, Medfield, Massachusetts). The measurement bias (mean difference between measurement and the known value) of the standard solutions with 21.5, 45, and 70 mm Hg of P_{CO_2}, using the Ciba-Corning 278 in our laboratory, were -0.9, -1, and -0.7 mm Hg (sample $n = 781$), respectively. The measurement precisions (standard deviation of bias) of P_{CO_2} for these solutions were 0.9, 1.3, and 1.4 mm Hg, respectively. All blood gas values were calculated at 37°C, since the body temperature change is negligible during a short period of exercise.[22] The carboxyhemoglobin level was measured at rest with a spectrophotometric oximeter (CO-Oximeter 270, Ciba-Corning, Medfield, Massachusetts). Whole blood lactate concentrations were also analyzed (1500 Sport, YSI, Yellow Springs, Ohio).

Measurements

$\dot{V}_{O_2}$ (mL/min), $\dot{V}_{CO_2}$ (mL/min), $\dot{V}_E$ (L/min), P_{ETCO_2}, other respiratory variables, and cardiovascular variables were measured. The anaerobic threshold is defined as the level of work just below that at which metabolic acidosis and the associated changes in gas exchange become manifest,[23] and was measured using the V-slope method.[24] The pH, P_{aCO_2}, P_{aO_2}, and standard bicarbonate of arterial blood samples were measured and calculated with a blood gas analyzer.

Statistical Analysis

The mean ± SD of each variable is shown unless otherwise specified. Bivariate and multivariable analyses were performed using the subject-specific linear mixed models, which took into account the potential correlations in the P_{aCO_2} within the same individual.[25] The predictive values and the coefficients of the fixed effects of the linear mixed models have the same interpretations as those in ordinary linear regression models.

Model Selection

Under the circumstances, with many candidate variables and their interactions, we began with a screening step. First, we performed an all possible subsets ordinary least squares regression procedure, including all demographic, anthropological, and noninvasive clinical measurements as the candidates, and the models provided approximate goodness-of-fit information. This step identified the best ten 3-variable, ten four-variable, and ten five-variable models, according to their performance of adjusted R^2 on the predictors.[26] In a second step, we then fit a series of linear mixed models, including the 3-, 4-, and 5-variable combinations identified in the first step. The Akaike information criterion, a goodness-of-fit measure, was calculated for each of the candidate models. A smaller Akaike information criterion stands for a better fit to the data.

Internal Validation

To evaluate the predictive ability, a leave-one-out cross-validation predictive error was calculated for each model.[27] In brief, the cross-validation predictive error was the square root of the sum of the square of the differences between each case's observed value (eg, the *i*th case's P_{aCO_2}) and predicted value, in which the predicted value was calculated using the equation excluding the case in model building (ie, the *i*th case was excluded in fitting the equation). One difference from an ordinary leave-one-out procedure is that, since there are 41 independent sampling units (individuals) each with 5–8 measurements, here the leave-one-out procedure left "an individual" out each time, instead of leaving "one observation" out. A smaller cross-validation predictive error stands for a better predictive ability for P_{aCO_2}. Thus the models with smaller Akaike

Table 1. Demographics and Lung Function of 41 Men With COPD*

	Mean ± SD	% Predicted
Age, y	65.3 ± 5.7	
Height, cm	165.1 ± 6.4	
Weight, kg	60.8 ± 11.4	
BMI, kg/m^2	22.2 ± 3.6	
Cigarette smoking, pack years	41.6 ± 19.5	
Oxygen cost diagram, absolute units	7.2 ± 1.4	
FVC, L	2.48 ± 0.66	80.6 ± 20.6
SVC, L	2.68 ± 0.66	92.8 ± 42.5
FEV_1, L	1.2 ± 0.47	50 ± 19
COPD Stage		
1 (n = 3)	2.24 ± 0.67	91 ± 8
2 (n = 17)	1.44 ± 0.07	63 ± 8
3 (n = 17)	1.0 ± 0.2	41 ± 6
4 (n = 4)	0.66 ± 0.13	23 ± 5
FEV_1/FVC, %	49 ± 13	
TLC, L	6.49 ± 1.03	134 ± 21
RV/TLC, %	61 ± 23	
D_{LCO}, mL/mm Hg/min	15.9 ± 5.5	69 ± 21
P_{Imax}, cm H_2O	68 ± 19	64 ± 17
P_{Emax}, cm H_2O	103 ± 23	51 ± 11
Carboxyhemoglobin, %	1.3 ± 0.9	

* After excluding 6 patients due to inadequate data collection for analysis.
BMI = body mass index
SVC = slow vital capacity
TLC = total lung capacity
RV = residual volume
D_{LCO} = diffusing capacity for carbon monoxide
P_{Imax} = maximum inspiratory pressure
P_{Emax} = maximum expiratory pressure

Table 2. Exercise Data and Arterial Blood Gas Analysis at Rest and at Peak Exercise in 41 Men With COPD*

	At Rest, mean ± SD	At Peak, mean ± SD
Work, watts	0 ± 0	89 ± 42
$\dot{V}_{O_2}$, L/min	0.44 ± 0.09	1.08 ± 0.32
$\dot{V}_{CO_2}$, L/min	0.4 ± 0.08	1.15 ± 0.38
Respiratory exchange ratio	0.91 ± 0.06	1.05 ± 0.1
Heart rate, beats/min	80 ± 13	133 ± 19
Heart rate, % of predicted maximum†	49 ± 7.4	83 ± 11
Oxygen pulse, mL/beat	4.8 ± 1.2	8.2 ± 2.3
Systolic blood pressure, mm Hg	174 ± 25	220 ± 31
Diastolic blood pressure, mm Hg	86 ± 12	100 ± 12
$\dot{V}_E$, L/min at BTPS	17.2 ± 3.2	38.8 ± 10.7
$\dot{V}_E$/MVV, %‡	55 ± 21	119 ± 38
V_T, L at BTPS	0.83 ± 0.2	1.21 ± 0.32
f, breaths/min	21.4 ± 4.6	32.5 ± 6.5
Borg score	0.9 ± 0.9	8.1 ± 2.5
$\dot{V}_E/\dot{V}_{O_2}$	39.8 ± 7.3	36.8 ± 8
$\dot{V}_E/\dot{V}_{CO_2}$	43.5 ± 7	35.1 ± 7.1
P_{ETCO_2}, mm Hg	37.4 ± 6.3	43.1 ± 8.2
P_{aCO_2}–P_{ETCO_2}, mm Hg	4 ± 3.5	2.4 ± 4.1
F_{ECO_2}, %	3 ± 0.5	3.8 ± 0.8
pH	7.38 ± 0.03	7.32 ± 0.04
P_{aCO_2}, mm Hg	41.4 ± 6.4	45.6 ± 7.7
P_{aO_2}, mm Hg	80.9 ± 12.7	70.5 ± 14.3
HCO_3^-, mEq/L	24.6 ± 2.7	23.5 ± 3.4
Lactate, mmol/L in whole blood	0.4 ± 0.2	3.3 ± 1.6

* After excluding 6 patients due to inadequate data collection for analysis. All comparisons between at rest and at peak exercise are very significant: all $P < .001$, except $\dot{V}_E/\dot{V}_{O_2}$ (P = .004).
† Predicted maximum heart rate = 220–age in years
‡ $\dot{V}_E$/MVV: 92.7% of patients reached ≥ 70% of $\dot{V}_E$/MVV
$\dot{V}_{O_2}$ = O_2 uptake
$\dot{V}_{CO_2}$ = CO_2 output
Oxygen pulse = $\dot{V}_{O_2}$/heart rate
BTPS = body temperature, ambient atmospheric pressure, and fully saturated
$\dot{V}_E$ = minute ventilation
MVV = maximum voluntary ventilation
V_T = tidal volume
f = respiratory frequency
P_{ETCO_2} = end-tidal P_{CO_2}
P_{aCO_2}–P_{ETCO_2} = difference between P_{aCO_2} and P_{ETCO_2}
F_{ECO_2} = fraction of mixed expired CO_2

information criterion and smaller cross-validation predictive error have priority to be selected. P value $< .05$ was considered statistically significant.

All the above procedures were carried out using statistical software (SAS 9.2, SAS Institute, Cary, North Carolina, and Origin 4.0, Microcal Software, Northampton, Massachusetts). A special SAS macro was generated for calculating the cross-validation predictive error.

Data Processing

To illustrate the validity of the derived equation for predicting P_{aCO_2}, differences between the measured and estimated P_{aCO_2} values during the loaded exercise were compared. Because of the variation among subjects in exercise duration and the number of arterial blood samples that were drawn, we interpolated the multiple P_{aCO_2} values from the start of exercise to the peak of exercise into 100 points for each subject, and then time aligned and averaged the P_{aCO_2} values at each time point of 10% of exercise duration for a group of patients, using Origin 4.0. To test the mean difference between the predicted and measured P_{CO_2}, averaging the mean differences over all subjects was conducted. The standard error, 95% CI, and P value to this mean difference were estimated by a linear mixed model to take into account the correlation within the subject.

Results

A total of 41 male patients were enrolled after excluding 6 patients with inadequate data collection for analysis. Most of the patients had a moderate to severe stage of COPD by the GOLD criteria, with moderate air-trapping and mild impairment of D_{LCO} and maximum expiratory pressure (Table 1).

Table 2 provides physiological data regarding subjects at rest and at peak exercise. Forty-six percent of the pa-

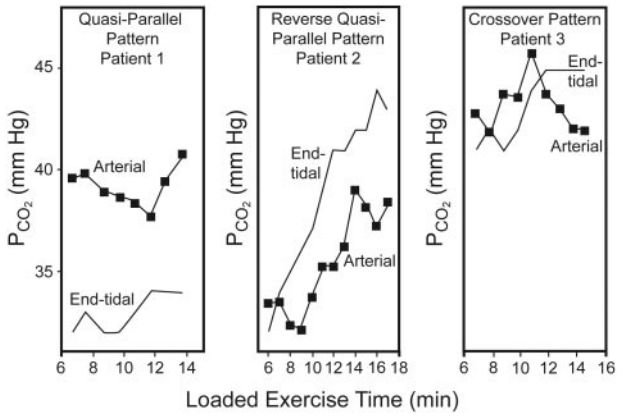

Fig. 1. CO_2 partial pressure measured with arterial blood gas analysis and end-tidal CO_2 analysis, in symptom-limited incremental exercise in 3 representative subjects. In the quasi-parallel pattern, both variables increased along with exercise and P_{aCO_2} was higher. In the reverse quasi-parallel pattern, both variables increased along with exercise and P_{aCO_2} was lower. In the cross-over pattern, both variables increased to some extent and then crossed over near the end of loaded exercise.

tients enrolled in this study achieved ≥ 85% of their maximal heart rate predicted, and 92.7% of patients achieved a ratio of $\dot{V}_E$ to maximum voluntary ventilation of ≥ 70% at peak exercise. Three patterns of relationship between P_{aCO_2} and P_{ETCO_2} in response to exercise were observed: quasi-parallel pattern ($n = 34$, 83%), reverse quasi-parallel pattern ($n = 4$), and cross-over pattern ($n = 3$) (Fig. 1). The patients with the quasi-parallel pattern were older (66 ± 5 y) and had lower SVC (2.6 ± 0.6 L), FEV_1 (1.0 ± 0.4 L), peak expiratory flow rate (2.7 ± 1.0 L/s), and D_{LCO} (15.2 ± 4.4 mL/min/mm Hg), by comparison across patients of the 3 patterns (all $P < .05$).

Univariate analysis revealed that there were 21 variables significantly correlating to P_{aCO_2} (Table 3). After applying multivariable linear mixed regression technique, the 5 models with the smallest leave-one-out cross-validation predictive error were listed in Table 4. Model 1 demonstrated both the smallest Akaike information criterion and leave-one-out cross-validation error. Comparisons between the different predictive models are also shown. In light of the above mentioned criteria, the best predicted equation is:

$$\text{Predicted } P_{aCO_2} = 23.71 + P_{ETCO_2} \times (0.9 - 0.01 \times D_{LCO} - 0.04 \times V_T) - 2.61 \times SVC - 0.04 \times MEP \quad \text{(Equation 1)}$$

This fitted equation used 306 observations in 41 patients. The Akaike information criterion was 1,099, and the leave-one-out cross-validation predictive error was 6.53. The units of P_{ETCO_2} were mm Hg, SVC L, maximum expiratory pressure cm H_2O, D_{LCO} mL/min/mm Hg, and V_T L.

Table 3. Univariate Analysis of the Potential Predictors of P_{aCO_2} in Response to Incremental Exercise in COPD ($n = 41$)

	Coefficient*	Akaike Information Criterion†	*P*
P_{ETCO_2}	0.68	1,213	< .001
F_{ECO_2}	4.65	1,237	< .001
$\dot{V}_E/\dot{V}_{CO_2}$	–0.41	1,366	< .001
Blood Pressure			
Systolic	0.08	1,376	< .001
Diastolic	0.18	1,420	< .001
Heart rate	0.08	1,420	< .001
$\dot{V}_{CO_2}$	0.00	1,429	< .001
$\dot{V}_{O_2}$/heart rate	0.93	1,429	< .001
$\dot{V}_E$	0.13	1,468	< .001
V_T	5.71	1,472	< .001
T_I	–7.30	1,478	< .001
f	12.85	1,488	< .001
$\dot{V}_E/\dot{V}_{O_2}$	–0.31	1,490	< .001
FVC	–4.41	1,538	.004
FEV_1	–5.60	1,538	.006
SVC	–4.35	1,539	.007
T_I/T_{tot}	15.16	1,539	.03
BMI	0.69	1,544	.02
RV/TLC	0.34	1,544	.006
MVV	–0.17	1,547	.03
Height	–0.33	1,547	.044

* The coefficient is the slope of the separate linear mixed model.
† For details, please refer to the text. A smaller Akaike information criterion stands for a better model fit for each model.
P_{ETCO_2} = end-tidal P_{CO_2}
F_{ECO_2} = fraction of mixed expired CO_2
$\dot{V}_E$ = minute ventilation
$\dot{V}_{CO_2}$ = CO_2 output
$\dot{V}_{O_2}$ = O_2 uptake
V_T = tidal volume
T_I = inspiratory time
f = respiratory frequency
SVC = slow vital capacity
T_I/T_{tot} = inspiratory time/total respiratory cycle time
BMI = body mass index
RV/TLC = residual volume/total lung capacity
MVV = maximum voluntary ventilation

Figure 2 shows the validity of the prediction equation based on the insignificant differences that were observed between the measured and estimated P_{aCO_2} values during the loaded exercise ($P > .05$). The mean for the measured P_{aCO_2} was 43.2 mm Hg, and the mean for the predicted P_{aCO_2} was 43.4 mm Hg. The mean difference between predicted P_{aCO_2} and measured P_{aCO_2} and its 95% CI were 0.19 and −0.2 to 0.59, respectively ($P = .34$). Figure 3 shows the validity of the prediction equation, based on the insignificant differences that were observed between the measured and estimated P_{aCO_2} values at each time point of the loaded exercise (all

Table 4. Multivariable Models for Predicting Dynamic P_{aCO_2} During Maximum Exercise in 41 Patients With COPD (blood samples $n = 306$)*

Model	Predictor	B0*	B1	B2	B3	B4	B5	Akaike Information Criterion	Akaike Information Criterion Rank	Cross-Validation Predictive Error	Cross-Validation Predictive Error Rank
1	P_{ETCO_2} SVC P_{Emax} $P_{ETCO_2} \times D_{LCO}$ $P_{ETCO_2} \times V_T$	23.71	0.90	–2.61	–0.04	–0.01	–0.04	1,099.0	1	6.53	1
2	P_{ETCO_2} P_{Emax} $P_{ETCO_2} \times$ SVC $P_{ETCO_2} \times D_{LCO}$ $P_{ETCO_2} \times V_T$	16.66	1.05	–0.04	–0.07	–0.00	–0.03	1,105.2	7	6.55	2
3	P_{ETCO_2} $\dot{V}_E/\dot{V}_{CO_2}$ P_{Emax} $P_{ETCO_2} \times$ SVC $P_{ETCO_2} \times D_{LCO}$	10.95	1.10	0.09	–0.04	–0.07	–0.01	1,103.3	5	6.64	3
4	P_{ETCO_2} $\dot{V}_E/\dot{V}_{CO_2}$ SVC P_{Emax} $P_{ETCO_2} \times D_{LCO}$	18.54	0.92	0.09	–2.75	–0.04	–0.01	1,099.5	2	6.88	4
5	P_{ETCO_2} P_{Emax} $P_{ETCO_2} \times$ SVC $P_{ETCO_2} \times D_{LCO}$ $P_{ETCO_2} \times$ age	18.45	0.77	–0.04	–0.08	–0.00	0.00	1,111.7	8	7.39	5

* B0 is the intercept and B1 through B5 are the slopes of the predictors of the linear mixed regression model (eg, for model 1, 0.90 is the coefficient for P_{ETCO_2}, –2.61 is the coefficient for SVC, and so on). A positive coefficient indicates a positive relationship between P_{aCO_2} and the variable, whereas a negative coefficient indicates a negative relationship. A smaller Akaike information criterion stands for a better fit, and a smaller cross-validation predictive error stands for less prediction error.

P_{ETCO_2} = end-tidal P_{CO_2}
SVC = slow vital capacity
P_{Emax} = maximum expiratory pressure
D_{LCO} = diffusing capacity for carbon monoxide
V_T = tidal volume
$\dot{V}_E$ = minute ventilation
$\dot{V}_{CO_2}$ = CO_2 output

$P > .05$). The standard errors of the estimated P_{aCO_2} ranged from 0.91 to 1.12 mm Hg.

Discussion

End-capillary P_{CO_2} is not equivalent to alveolar P_{CO_2}.[28,29] It might be anticipated that an individual patient's P_{aCO_2} may not be equal to a more readily measurable P_{ETCO_2} under certain physiologic conditions. Some studies in adults,[14] including elderly individuals, both at rest and during exercise,[11,12] as well as a single study of patients with COPD,[13] have shown that the P_{aCO_2} correlates well with P_{ETCO_2}. However, it has been difficult to predict P_{aCO_2} from P_{ETCO_2}, due to the increase in CO_2 loading to the lung, the inherent inhomogeneous ventilation/perfusion matching, the increased V_D/V_T, and the cyclic breathing patterns seen particularly in the elderly and in patients with COPD performing exercise. In this study we found that P_{ETCO_2} remained the paramount predictor for P_{aCO_2}, while the diffusing capacity, the vital capacity, the V_T, and the expiratory muscle strength were inversely related to P_{aCO_2} (see Table 4).

Diffusing capacity includes alveolar-capillary membranous diffusing capacity and pulmonary blood volume (ie, pulmonary circulatory capacity). Diffusing capacity for CO is little affected by alveolar-capillary membranous diffusing capacity, except when carbonic anhydrase is inhibited by drugs such as acetazolamide.[30] The inverse relationship between D_{LCO} and P_{aCO_2} is believed to be due to a poorer pulmonary circulatory capacity related to COPD. The inverse relationship between vital capacity or V_T and P_{aCO_2} is explicitly explained by the Bohr equation. Expiratory muscle strength is negatively related to residual

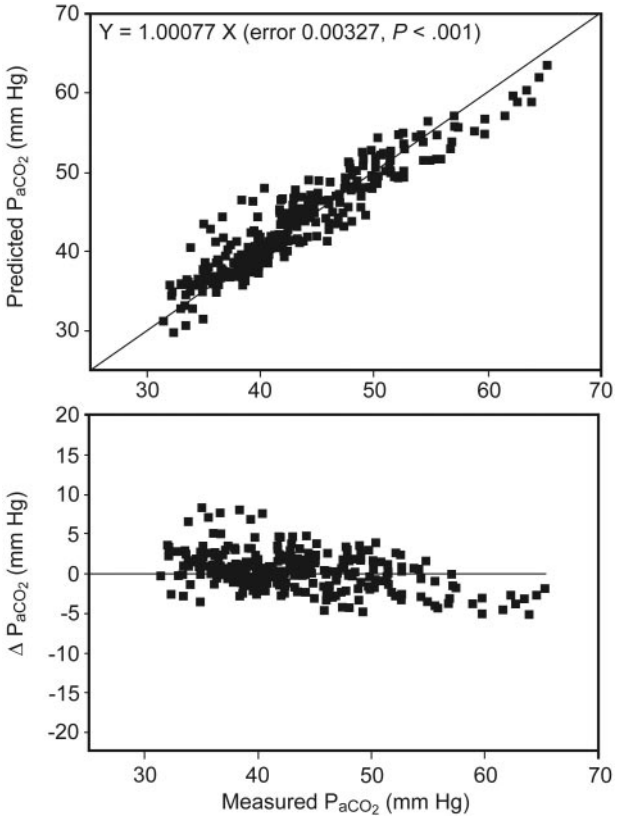

Fig. 2. Upper panel: Scattergram of measured P_{aCO_2} and predicted P_{aCO_2} using Equation 1. The oblique solid line indicates the line of identity. The oblique dotted line indicates the regression line through zero. Lower panel: Absolute deviations plotted against the measured P_{aCO_2}. Each symbol shown represents one blood sample of the 41 subjects. Multiple blood samples were drawn from each subject. ΔP_{aCO_2} is the difference between predicted P_{aCO_2} and measured P_{aCO_2}. The differences between each pair of P_{aCO_2} were insignificant ($P = .34$).

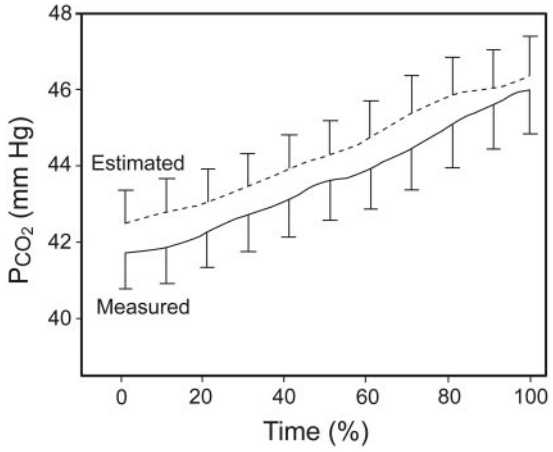

Fig. 3. The P_{aCO_2} measured during the symptom-limited cycling exercise and the estimated P_{aCO_2}, using Equation 1 of our study. Data shown are averaged for 41 subjects. The bars show the standard error at the start of loaded exercise, every 10% of loaded exercise, and at the peak of exercise. The differences between each pair of P_{CO_2} were insignificant. None of the differences are significant.

volume,[31] and thereby positively related to vital capacity, and therefore inversely related to P_{aCO_2}.

By jointly considering these 5 variables and their interactions, the prediction of P_{aCO_2} becomes much better than with any variable alone, because the model fits in terms of lower Akaike information criterion values and has a better predictive ability in terms of lower leave-one-out cross-validation predictive errors.

The carboxyhemoglobin had little effect on the P_{aCO_2} prediction in our study, although it has been reported that carboxyhemoglobin levels increase the difference between P_{aCO_2} and P_{ETCO_2} or V_D/V_T.[32] The discrepancies between the 2 studies might be due to the differences in study design. Hirsch et al studied the acute effect of smoking on cardiovascular function of their participants, while we studied the chronic effects of smoking.

It is hard to predict dynamic P_{aCO_2} with P_{ETCO_2} alone, because the changes in P_{ETCO_2} or P_{aCO_2} occur as a function of exercise intensity and are nonlinear. During a ramp-pattern incremental exercise test in normal subjects, both P_{aCO_2} and P_{ETCO_2} increase mildly from the start of loaded exercise to the point of the anaerobic threshold, followed by a leveling-off due to isocapnic buffering, followed by a lower P_{aCO_2} and P_{ETCO_2} due to respiratory compensation.[33,34] The differences between P_{aCO_2} and P_{ETCO_2} are different at different levels of exercise intensity, such as being positive at rest and negative at peak exercise. Based on our findings, another reason that dynamic P_{aCO_2} values are hard to predict with P_{ETCO_2} alone is that there are 3 patterns of the relationship between change in P_{aCO_2} and P_{ETCO_2} (see Fig. 1).

One may argue that our predictive equation is not the only noninvasive method to yield P_{aCO_2} values. A noninvasive diagnostic tool such as transcutaneous P_{CO_2} monitoring attempted to measure P_{aCO_2} during anesthesia or exercise.[2,5,6] The transcutaneous P_{CO_2} measured with CO_2 electrodes has been reported to be slow in response time and cannot reflect transient changes noted during different levels of work load exercise or during a 2-min or less incremental exercise evaluation.[6,7]

The P_{ETCO_2} trend of the 9-panel plot is a very useful clue in the diagnosis of right-to-left shunt in dyspneic patients.[35] Incorporating the estimated P_{aCO_2} values from our derived predictive equation might make it simpler for a clinician or investigator to detect high ventilation/perfusion mismatch, a right-to-left shunt, or the presence of hyperventilation. Hyperventilation may cause both P_{aCO_2} and P_{ETCO_2} to be low, while the high ventilation/perfusion mismatch or right-to-left shunt may cause the P_{aCO_2} to be high and the P_{ETCO_2} to be low, thereby augmenting $P_{aCO_2} - P_{ETCO_2}$.

The prediction performance of our derived equation and the previously reported data by Liu et al have the same P value ($< .001$), but our derived equation has a lower standard error of the estimate (0.91–1.12 mm Hg vs 2.8 mm Hg).[13] Unfortunately, we cannot compare the R^2, due to the different statistical methods, or the calculated P_{aCO_2} values, due to the equations not being provided by Liu et al.[13]

One study reported that

$$F_{ACO_2} = F_{ICO_2} + 1.136 \times \dot{V}_{CO_2}/\dot{V}_A$$

(where F_{ACO_2} is the fraction of alveolar CO_2, F_{ICO_2} is the fraction of inspired CO_2, $\dot{V}_{CO_2}$ is carbon dioxide production, and $\dot{V}_A$ is alveolar ventilation), assuming P_{aCO_2} equal to alveolar P_{CO_2} throughout the breathing cycle in young healthy individuals during dynamic exercise.[36] They reported that the mean difference and the upper and lower limits of agreement between measured and simulated P_{aCO_2} were -0.004, $+0.84$, and -0.84 mm Hg, respectively. The authors reported that the $\dot{V}_A$, which involves V_D/V_T, can only be determined by inserting an arterial catheter and drawing multiple arterial blood samples for calculation.

Study Limitations

A male-only study group diagnosed with COPD prevents application of our findings to the general population. Given the current available data, a multiple regression with the leave-one-out method is a useful way to derive and validate our equation. However, blood gas analysis remains the best way to ascertain EIH, $P_{aCO_2} - P_{ETCO_2}$, or V_D/V_T. To best validate the usefulness of our derived equation, further studies with another patient population are needed.

Another concern is whether or not we increased the sample size while using the interpolation technique to process the data. We interpolated the multiple P_{aCO_2} values because the fitness of each subject might not be identical, and the volitional symptom-limited exercise test was applied so that the exercise durations were different. For comparison at each 10% of exercise time, there were 41 pairs of data: one for measurements and the other for predictions. This technique did not increase the sample size for each comparison. Although the Bland-Altman plot (see Fig. 2) showed an insignificant difference between predicted P_{aCO_2} and measured P_{aCO_2} during the loaded exercise ($P = .34$), there was a trend that P_{aCO_2} is overestimated if P_{aCO_2} is < 40 mm Hg.

Conclusions

To our knowledge, this study is the first to report equations for dynamic estimation of P_{aCO_2} noninvasively in patients with COPD performing a ramp-pattern exercise test. With a similar average and a small error of the estimate between the measured and estimated P_{aCO_2}, we conclude that our predictive equations forecast the P_{aCO_2} accurately and the multiple P_{aCO_2} values estimated from our derived equation can be used to contrast with the P_{ETCO_2} trend of a 9-panel plot. The estimated $P_{aCO_2} - P_{ETCO_2}$ and EIH can then be readily appreciated.

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