End-Tidal Carbon Dioxide as a Prognostic Feature in Pulmonary Arterial Hypertension

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Abstract

Rationale: Pulmonary arterial hypertension (PAH) is characterized in part by increased dead space ventilation, which can be estimated noninvasively at the bedside by measurement of end-tidal CO₂ (ETCO₂).

Objectives: Prior work has demonstrated that ETCO₂ is lower in patients with PAH than in control patients, but whether ETCO₂ has prognostic value is unknown. We hypothesized that lower measurements of ETCO₂ in patients with PAH correlate with worse long-term outcomes.

Methods: Patients with PAH seen in our referral clinic were prospectively recruited for ETCO₂ measurement between September 2009 and February 2010. Vital status as of July 2015 was documented using medical records and the Social Security Death Index.

Results: Eighty-two patients were followed for a median of 60 months. Twenty-six patients died, and two were lost to

follow-up. Patients who died were more likely to be older (58.5 ± 14.9 vs. 47.6 ± 12.2 yr; $P < 0.05$) and to have shorter 6-minute walk distance (296 ± 127 vs. 401 ± 92 m; $P < 0.05$). Mean ETCO₂ in survivors was 30.5 ± 4.8 mm Hg, whereas mean ETCO₂ in patients who died was 27.1 ± 4.2 mm Hg ($P = 0.004$). After stratification by median baseline ETCO₂ of 29 mm Hg, survival in each group was analyzed. Patients with lower ETCO₂ had shorter survival ($P = 0.006$). Cox regression analysis with ETCO₂ as a continuous variable revealed the hazard ratio to be 0.88 (95% confidence interval, 0.80–0.97; $P = 0.006$). In 52 patients with more than one measurement a median of 17 months apart, ETCO₂ was unchanged.

Conclusions: Our single-center data suggest that lower ETCO₂ is associated with shorter survival and that ETCO₂ is stable over time in patients with PAH.

Keywords: end-tidal carbon dioxide; pulmonary hypertension; survival

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Pulmonary arterial hypertension (PAH) is a highly morbid disease, though modern registry data suggest that some patients may have a more favorable survival than historical control subjects (1, 2). Noninvasive tools that are available at the bedside are needed to identify patients at high risk of death because

currently available prognostic metrics such as right heart catheterization, brain natriuretic peptide, and echocardiography are costly, time consuming, and not always readily available.

PAH is a disease of vascular obstruction resulting in increased dead space secondary

to obstruction of pulmonary arterioles, leading to alveoli that are ventilated but not perfused. The PCO₂ in normal, perfused alveoli approximates central venous PCO₂ (on average, about 40 mm Hg). In alveoli that are ventilated but not perfused (i.e., dead space), the PCO₂ is near 0 mm Hg.

As dead space increases, the end-tidal CO₂ (ETCO₂) decreases as air from both perfused and unperfused alveoli mix in the large airways upon exhalation.

Prior publications by our group and others have shown that ETCO₂ is reduced in PAH (2, 3) compared with control subjects and patients with pulmonary venous hypertension (World Health Organization [WHO] class II PAH). As the fraction of pulmonary arterial obstruction increases in advancing PAH, ETCO₂ should fall proportionally. Thus, the degree of ETCO₂ suppression may be a surrogate for the extent of pulmonary vascular disease and therefore may have prognostic value. Further, our prior data suggested that with new initiation of intravenous epoprostenol, ETCO₂ increased; however, it is unknown if ETCO₂ is unchanged over time in a cohort of patients largely on stable therapy.

We hypothesized that ETCO₂ is stable over time in PAH and that lower ETCO₂ is associated with higher mortality. We tested this hypothesis in a cohort of patients with PAH with ETCO₂ measurements who were followed prospectively at the Vanderbilt University Center for Pulmonary Vascular Disease. These data were partially presented previously in abstract form (4).

Methods

Study Design

We conducted a single-center, prospective study of ETCO₂ in patients with PAH. The Vanderbilt University Medical Center Institutional Review Board (Nashville, TN) approved the study, and all subjects gave informed consent (IRB 070270). Previous results of this work have been published, but the analyses presented here have not been reported previously (2).

Setting and Population

All patients over the age of 18 years with pulmonary hypertension seen at the Vanderbilt University Center for Pulmonary Vascular Disease clinic were offered enrollment between September 2009 and February 2010 (2). Patients who presented for a return visit during that time frame had ETCO₂ measurement repeated.

Patients were evaluated according to standard criteria to identify WHO classes I–V PAH. This analysis included only patients with group 1 PAH. PAH was defined as previously described (2) by physicians experienced in

pulmonary hypertension evaluation (I.M.R., A.R.H.) and further required right heart catheterization with a mean pulmonary arterial pressure greater than or equal to 25 mm Hg and a pulmonary capillary wedge pressure less than or equal to 15 mm Hg (5).

Measurements

ETCO₂ was measured using the Nellcor NPB-75 handheld capnograph (Nellcor Puritan Bennett/Covidien, Boulder, CO) (6). Trained testers who were blinded to diagnosis obtained the ETCO₂ measurement. Five ETCO₂ measurements were recorded after the patient rested for at least 5 minutes prior to the 6-minute walk test, as previously described (2). The mean of these five measurements was used for analysis. Reproducibility and variability of ETCO₂ measurements using the Nellcor NPB-75 handheld capnograph have been described previously (2). Six-minute walk tests were performed per the American Thoracic Society criteria (7).

Demographic data, including age, sex, body mass index (BMI), diagnosis, comorbidities (including diabetes mellitus, coronary artery disease, hypertension, and hyperlipidemia), New York Heart Association (NYHA) functional class, and 6-minute walk distance, were collected upon enrollment. Pulmonary function test data and right heart catheterization data were collected around the time of enrollment.

Follow-Up

Routine practice at the Center for Pulmonary Vascular Disease was initially and approximately annual right heart catheterization and 6-minute walk testing approximately every 3–6 months unless clinically indicated. When patients were seen within the enrollment window, ETCO₂ was remeasured. Patients who did not return for follow-up or did not have repeat 6-minute walk testing did not have repeat

Table 1. Demographics of the patients, separated by vital status at follow-up

	Alive (n = 56)	Dead (n = 26)	P Value
Age, yr	47.6 ± 12.2	58.5 ± 14.9	0.0013
Sex, M, F	17 (30.4%), 39 (69.6%)	6 (23.1%), 20 (76.9%)	0.60
BMI, kg/m ²	29.4 ± 6.6	26.3 ± 4.7	0.11
Hypertension, no	15 (26.8%)	9 (34.6%)	0.60
Hyperlipidemia, no	16 (28.6%)	5 (19.2%)	0.43
Diabetes mellitus type 2, no	10 (17.9%)	2 (7.7%)	0.32
Coronary artery disease, no	3 (5.4%)	1 (3.8%)	1.00
NYHA functional class			
I/II	42 (75%)	10 (38.5%)	0.0014
III/IV	14 (25%)	16 (61.5%)	
PAH diagnosis			
HPAH/IPAH	27 (48.2%)	11 (42%)	0.03
CTD	11 (19.6%)	12 (46%)	
CHD	14 (25%)	1 (3.8%)	
Other	4 (7.5%)	2 (7.7%)	
Medications			
None or CCB	6 (10.7%)	2 (7.7%)	0.46
ERA	10 (17.9%)	2 (7.7%)	
PDE5	6 (10.7%)	1 (3.8%)	
Prostacyclin	8 (14.3%)	4 (15.4%)	
Combination therapy	26 (46.4%)	17 (65.4%)	
6-min walk distance, m	401.4 ± 91.7	296.3 ± 127.0	0.0003
FEV ₁ [*] , %	75.1 ± 16.2	68.8 ± 19.0	0.20
FVC [†] , %	79.7 ± 17.0	74.5 ± 18.3	0.26
DL _{CO} [‡] , %	68.3 ± 19.5	50.6 ± 27.4	0.0008

Definition of abbreviations: BMI = body mass index; CCB = calcium channel blocker; CHD = congenital heart disease; CTD = connective tissue disease; DL_{CO} = diffusing capacity of the lung for carbon monoxide; ERA = endothelin receptor antagonist; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5 inhibitor. Combination therapy included ERA + prostaglandin, PDE5 + prostaglandin, ERA + PDE5 + prostaglandin, CCB + PDE5, and CCB + ERA.

Data are presented as mean ± SD unless otherwise noted.

*Alive (n = 44); dead (n = 24).

†Alive (n = 43); dead (n = 24).

‡Alive (n = 47); dead (n = 23).

ETCO₂ measurements. When available, these data were extracted from the medical record. Vital status as of July 31, 2015, was documented using the medical record and the Social Security Death Index. Survivors were censored on the date of last medical contact. The number of months between enrollment and the last medical contact or death was calculated for each patient. If the date of death was unknown but the month was known (three patients), the first day of the month of death was used for the purpose of follow-up calculations.

Statistical Analysis

All values are reported as mean $\pm$ SD and categorical variables as absolute value and percent. Between-group differences were calculated using the Mann-Whitney *U* test, chi-square test, or one-way analysis of variance. Correlation coefficients were calculated using Spearman's method. Time-to-event analyses were performed using the Kaplan-Meier log-rank test and Cox regression to assess the impact of ETCO₂ on time to death. We prespecified a Cox regression analysis comparing upper and lower median ETCO₂ values, controlling for age and sex because these variables are known to influence survival and clinical course in patients with PAH. Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA) software.

Results

Study Population

A total of 84 patients with PAH were enrolled in the study. Diagnoses included idiopathic PAH (*n* = 33), heritable PAH (*n* = 6), connective tissue disease-associated PAH (*n* = 23), portopulmonary hypertension (*n* = 1), corrected or simple congenital heart disease-associated PAH (*n* = 15), and other PAH (*n* = 6). Two patients were lost to follow-up. The other 82 patients were followed for a median of 60 (interquartile range, 47–63) months. In total, 26 of 82 patients died during the follow-up period.

Demographic differences between those who died during follow-up and those who were still alive are shown in Table 1. Patients who died were more likely to be older (58.5 ± 14.9 vs. 47.6 ± 12.2 yr; $P < 0.05$) and to have shorter 6-minute walk distances

(296 ± 127 vs. 401 ± 92 m; $P < 0.05$). There was no significant difference between the number of men and women in the two groups, nor was there a difference in BMI or associated comorbidities. Patients who died were more likely than survivors to have heritable or connective tissue disease-associated PAH and less likely than survivors to have congenital heart disease-associated PAH. There was no significant difference in the PAH-directed treatments of the two groups. Patients who died during follow-up were more likely to be in NYHA functional class III or IV at baseline measurement than those who were still alive ($P < 0.05$). ETCO₂ was significantly higher in survivors than in those patients who died (30.5 ± 4.8 vs. 27.1 ± 4.2 mmHg; $P = 0.004$) (Figure 1). In patients with available pulmonary function test data (*n* = 71 [86.6%]), diffusing capacity of the lung for carbon monoxide (DL_{CO}) was significantly

higher in survivors than in those who had died at follow-up, whereas there were no differences in percent predicted FEV₁ or FVC. ETCO₂ correlated weakly with DL_{CO} ($r^2 = 0.28$; $P = 0.0177$) (Figure 2).

Right heart catheterization data were available for 81 patients (Table 2). Median time between ETCO₂ measurement and cardiac catheterization was 7 (interquartile range, 3–21) months. Mean right atrial pressures, pulmonary arterial systolic pressures, mean pulmonary arterial pressures, pulmonary capillary wedge pressures, pulmonary vascular resistance, and Fick cardiac indices were not significantly different between patients who were alive or dead at follow-up ($P > 0.05$ for all).

To test the stability of ETCO₂ measurement over time, we examined patients with at least two measurements over the course of the study. There were 52 patients with more than one measurement a median of 17 months

Figure 1. Mean end-tidal carbon dioxide pressure (ETCO₂) based on vital status at follow-up. Data are presented as mean $\pm$ SD. * $P = 0.004$ by Mann-Whitney *U* test.

Figure 2. Correlation of diffusing capacity of the lung for carbon monoxide (DL_{CO}) with end-tidal carbon dioxide pressure (ETCO₂). Spearman's test was used to determine the correlation. $r^2 = 0.28$; * $P = 0.0177$.

Table 2. Initial right heart catheterization data, separated by vital status at follow-up

	Alive (n = 54)	Dead (n = 26)	P Value
RAP, mm Hg	6.9 ± 5.1	8.4 ± 6.3	0.36
mPAP*, mm Hg	52.4 ± 16.0	46.0 ± 14.5	0.10
PCWP, mm Hg	8.9 ± 3.9	8.4 ± 5.1	0.47
PVR†, Wood units	9.6 ± 5.4	9.0 ± 4.0	0.99
CI†, Fick index, L/min/m ²	2.6 ± 0.9	2.5 ± 0.9	0.68

Definition of abbreviations: CI = cardiac index; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Data are presented as mean ± SD.

*Alive (n = 55); dead (n = 26).

†Alive (n = 52); dead (n = 26).

apart. In this cohort, ET_{CO₂} was unchanged (29.4 ± 5.0 vs. 28.4 ± 5.2 mm Hg; *P* = 0.25), including when analyzed separately by vital status. The change in ET_{CO₂} between enrollment and follow-up measurements was not significantly different between patients receiving oral therapy versus those patients receiving prostaglandins (either alone or in combination with oral therapy) at the time of enrollment in this study (n = 50; *P* = 0.80).

To determine if there was a difference in survival between patients with low ET_{CO₂} and those with preserved ET_{CO₂}, we separated the entire cohort according to the median ET_{CO₂} of 29 mm Hg. We found that there was no significant difference in age, sex, presence of comorbidities (hypertension, hyperlipidemia, coronary artery disease, or diabetes mellitus), 6-minute walk distance, types of PAH, or therapies received between the two groups (Table 3). BMI was significantly higher in patients with ET_{CO₂} greater than 29 mm Hg (*P* = 0.04). Despite relatively similar demographics, there were differences in hemodynamics. Specifically, pulmonary capillary wedge pressure was higher and pulmonary vascular resistance was lower in the patients with higher ET_{CO₂} readings (*P* < 0.05) (Table 4). Mean right atrial pressures, pulmonary artery systolic pressures, mean pulmonary arterial pressures, and Fick cardiac indices were not significantly different between the two groups (*P* > 0.05 for all). After stratification by median ET_{CO₂} of 29 mm Hg, survival in each group was analyzed with a Kaplan-Meier curve (Figure 3). Patients with lower ET_{CO₂} had a median survival of 58 months as compared with 61 months in patients with higher ET_{CO₂} (*P* = 0.006).

Kaplan-Meier curves stratified by upper and lower median ET_{CO₂} are shown in

Figure 3 (*P* = 0.006 by log-rank test). Cox regression analysis comparing upper and lower median ET_{CO₂} values adjusted for age and sex revealed a hazard ratio (HR) for the lower median of 3.13 (95% confidence interval [CI], 1.2–8.0; *P* = 0.017). Cox regression analysis with ET_{CO₂} as a continuous variable adjusted for age and sex revealed an HR of 0.88 (95% CI, 0.80–0.97; *P* = 0.006); thus, the risk of death decreased

by 12% for every 1-mm Hg increase in ET_{CO₂}. We were limited in the number of covariates for which we could adjust without overfitting the model, because only 26 deaths occurred during follow-up in our cohort. Therefore, adjustment for additional covariates was exploratory. After adjustment for age, sex, and DL_{CO}, the relationship between ET_{CO₂} and survival was no longer significant (HR, 0.91; 95% CI, 0.82–1.01; *P* = 0.085). When adjusting for age, sex, and 6-minute walk distance, we found that the association between ET_{CO₂} and survival trended toward statistical significance (HR, 0.91; 95% CI, 0.83–1.00; *P* = 0.06). However, after adjusting for age, sex, and serum bicarbonate levels as a surrogate for acid–base status, we observed that the association between ET_{CO₂} and survival persisted (HR, 0.88; 95% CI, 0.79–0.98; *P* = 0.017).

To determine what was different between those patients who had improvement in their ET_{CO₂} and those who had a decrease in their ET_{CO₂}, the cohort was separated into three groups on the basis of a mean ET_{CO₂} change of –1 mm Hg with

Table 3. Demographic data, separated by median end-tidal carbon dioxide pressure

	ET _{CO₂} ≤ 29 mm Hg (n = 46)	ET _{CO₂} > 29 mm Hg (n = 36)	P Value
Age, yr	52.7 ± 14.8	49.0 ± 12.7	0.27
Sex, M, F	15 (32.6%), 31 (67.4%)	8 (22.2%), 28 (77.8%)	0.33
BMI, kg/m ²	26.9 ± 4.7	30.4 ± 7.3	0.04
Hypertension, no	14 (30.4%)	10 (27.8%)	0.81
Hyperlipidemia, no	13 (28.3%)	8 (22.2%)	0.62
Diabetes mellitus type 2, no	4 (8.7%)	8 (22.2%)	0.12
Coronary artery disease, no	2 (4.3%)	2 (5.6%)	1.00
NYHA functional class			
I/II	29 (63.0%)	23 (63.9%)	1.0
III/IV	17 (37.0%)	13 (36.1%)	
PAH diagnosis			
HPAH/IPAH	18 (39.1%)	20 (55.6%)	0.50
CTD	14 (30.4%)	9 (25.0%)	
CHD	10 (21.7%)	5 (13.9%)	
Other	4 (8.7%)	2 (5.6%)	
Medications			
None or CCB	2 (4.3%)	6 (16.7%)	0.10
ERA	7 (15.2%)	5 (13.9%)	
PDE5	2 (4.3%)	5 (13.9%)	
Prostacyclin	6 (13.0%)	6 (16.7%)	
Combination therapy	29 (63.0%)	14 (38.9%)	
6-min walk distance, m	362.5 ± 114.7	375.2 ± 115.4	0.42

Definition of abbreviations: BMI = body mass index; CCB = calcium channel blocker; CHD = congenital heart disease; CTD = connective tissue disease; ERA = endothelin receptor antagonist; ET_{CO₂} = end-tidal carbon dioxide pressure; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5 inhibitor.

Data are presented as mean ± SD unless otherwise noted.

Combination therapy included ERA + prostaglandin, PDE5 + prostaglandin, ERA + PDE5 + prostaglandin, CCB + PDE5, and CCB + ERA.

Table 4. Initial hemodynamic data, separated by median end-tidal carbon dioxide pressure

	ETCO ₂ ≤ 29 mm Hg (n = 45)	ETCO ₂ > 29 mm Hg (n = 35)	P Value
RAP, mm Hg	6.9 ± 5.6	7.9 ± 5.4	0.32
mPAP*, mm Hg	52.4 ± 16.0	47.6 ± 15.2	0.39
PCWP, mm Hg	8.2 ± 4.6	9.5 ± 3.8	0.04
PVR†, Wood units	10.6 ± 5.3	7.9 ± 4.1	0.02
CI‡, Fick index, L/min/m ²	2.4 ± 0.9	2.8 ± 1.0	0.11

Definition of abbreviations: CI = cardiac index; ETCO₂ = end-tidal carbon dioxide pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Data are presented as mean ± SD.

*ETCO₂ less than or equal to 29 mm Hg (n = 46).

†ETCO₂ less than or equal to 29 (n = 43).

‡ETCO₂ less than or equal to 29 (n = 44); ETCO₂ greater than 29 (n = 34).

an SD of 5.5 mm Hg; patients who had an increase in ETCO₂ by at least 5 mm Hg, patients who had a decrease in ETCO₂ by at least 5 mm Hg, and patients who had an increase or decrease in ETCO₂ by less than 5 mm Hg. There was no significant difference in the demographics of these groups, including age, sex, BMI, and comorbidities (Table 5). The numbers were too small to compare types of PAH and therapies (Table 5). There were also no significant differences in the pulmonary function test data and right heart catheterization data that were analyzed among the three groups (Table 5).

We also compared ETCO₂ measurements among NYHA functional classes at enrollment and noted no significant difference in ETCO₂ between

groups (Figure 4). (Note that, for analysis, the NYHA functional classes III and IV were grouped together because only one patient was classified as NYHA functional class IV.)

Discussion

In this study, we have shown that ETCO₂, a safe, simple, and inexpensive measurement, is stable over time and that lower values are associated with increased mortality in patients with PAH. We also showed that DL_{CO} correlates with ETCO₂, suggesting potentially similar insight into the degree of pulmonary vascular obstruction in patients with PAH. Our data suggest that this readily available bedside test may be a physiologically relevant marker of poor prognosis in PAH.

Identifying patients with PAH at high risk of mortality has proved to be challenging. Many of the tests used to determine the severity of the disease are expensive, invasive, and time consuming (i.e., right heart catheterization or echocardiography). Some metrics are available at the bedside, including important demographic predictors such as age, sex, 6-minute walk distance, and type of PAH, but these give limited insight into the severity of pulmonary vascular obstruction. Measuring ETCO₂ is an inexpensive, noninvasive, quick test that can be performed at the bedside and, on the basis of our data, may offer valuable information regarding disease severity. Consistent with prior publications, older patients and those with shorter 6-minute walk distances and higher NYHA functional classes had worse outcomes in our sample (1, 8). After controlling for age, we found that ETCO₂ remained an independent predictor of increased mortality, and after adjustment for 6-minute walk distance, there was a strong trend toward persistent significance, suggesting that ETCO₂ may offer information additional to that of these more traditional, readily available metrics. Further, in patients who cannot perform 6-minute walk testing, ETCO₂ may be a useful prognostic tool.

Our prior work demonstrated that ETCO₂ correlated with pulmonary vascular resistance and cardiac index at enrollment, traditional hemodynamic markers of PAH severity, and we now show the role that ETCO₂ may have in identifying high-risk patients with PAH (2). We have previously demonstrated that ETCO₂ increases after initiation of therapy with intravenous prostaglandins in a small cohort of patients. In this larger cohort treated chronically with oral and prostaglandin therapies, we found that ETCO₂ was stable over time. The difference likely reflects the new start of intravenous epoprostenol reported in the prior publication and, perhaps, reduced capacity of oral therapies to improve cardiac output, a known determinant of ETCO₂ (9, 10).

COPD, left ventricular failure, and PAH are all characterized by $\dot{V}/\dot{Q}$ mismatch, increased dead space, and decreased ETCO₂ (11). The effect of interstitial lung disease on ETCO₂ is unknown. Prior studies have demonstrated a correlation between lower ETCO₂ and the severity of cardiac disease and have also demonstrated that lower ETCO₂ in this population correlates with higher New York Heart Association functional class

Figure 3. Kaplan-Meier survival curve with survival as a function of baseline end-tidal carbon dioxide pressure (ETCO₂). *P = 0.006. Numbers of subjects at risk at 0, 20, 40, and 60 months are presented below the curve.

Table 5. Demographic data, separated by change in end-tidal carbon dioxide pressure

	Decrease in ETco ₂ ≥ 5 mm Hg (n = 11)	Increase or Decrease in ETco ₂ by <5 mm Hg (n = 33)	Increase in ETco ₂ ≥ 5 mm Hg (n = 8)	P Value
Age, yr	49.3 ± 15.8	47.6 ± 14.7	55.8 ± 13.8	0.32
Sex				
M	3 (27.3%)	8 (24.2%)	3 (37.5%)	0.75
F	8 (72.7%)	25 (75.8%)	5 (62.5%)	
BMI, kg/m ²	28.8 ± 5.2	28.4 ± 6.7	24.9 ± 3.1	0.19
Hypertension, no	2 (18.2%)	7 (21.2%)	1 (12.5%)	0.85
Hyperlipidemia, no	4 (36.4%)	8 (24.2%)	1 (12.5%)	0.49
Diabetes mellitus type 2, no	3 (27.3%)	6 (18.2%)	0 (0.0%)	0.29
Coronary artery disease, no	1 (9.1%)	2 (6.1%)	1 (12.5%)	*
NYHA functional class				
I/II	6 (54.5%)	23 (69.7%)	5 (62.5%)	0.65
III/IV	5 (45.5%)	10 (30.3%)	3 (37.5%)	
PAH diagnosis				
HPAH/IPAH	6 (54.5%)	15 (45.5%)	1 (12.5%)	*
CTD	3 (27.3%)	6 (18.2%)	5 (62.5%)	
CHD	2 (18.2%)	8 (24.2%)	2 (25%)	
Other	0 (0.0%)	4 (12.1%)	0 (0.0%)	
Medications				
None or CCB	2 (18.2%)	1 (3.0%)	0 (0.0%)	*
ERA	1 (9.1%)	6 (18.2%)	1 (12.5%)	
PDE5	1 (9.1%)	2 (6.1%)	0 (0.0%)	
Prostacyclin	1 (9.1%)	7 (21.2%)	1 (12.5%)	
Combination therapy	6 (54.5%)	17 (51.5%)	6 (75.0%)	
6-min walk distance, m	395.8 ± 87.8	389.8 ± 105.9	382.8 ± 86.0	0.94
FEV ₁ [†] , %	81.7 ± 17.3	70.2 ± 14.6	67.9 ± 12.5	0.17
FVC [†] , %	88.2 ± 14.8	76.2 ± 13.4	74.9 ± 17.2	0.11
DL _{CO} [‡] , %	69.2 ± 17.9	66.6 ± 27.7	61.5 ± 22.8	0.77
RAP [§] , mm Hg	9.1 ± 6.3	6.6 ± 5.3	6.7 ± 6.2	0.43
mPAP, mm Hg	46.7 ± 11.7	55.1 ± 15.9	47.0 ± 16.7	0.18
PCWP, mm Hg	10.7 ± 4.5	8.2 ± 4.9	8.1 ± 4.4	0.29
PVR , Wood units	7.2 ± 3.5	11.0 ± 6.0	10.9 ± 4.5	0.12
CI [¶] , Fick index, L/min/m ²	2.8 ± 1.3	2.4 ± 0.7	2.0 ± 0.6	0.26

Definition of abbreviations: BMI = body mass index; CCB = calcium channel blocker; CHD = congenital heart disease; CI = cardiac index; CTD = connective tissue disease; DL_{CO} = diffusing capacity of the lung for carbon monoxide; ERA = endothelin receptor antagonist; ETco₂ = end-tidal carbon dioxide pressure; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE5 = phosphodiesterase type 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Combination therapy included ERA + prostaglandin, PDE5 + prostaglandin, ERA + PDE5 + prostaglandin, CCB + PDE5, and CCB + ERA.

Data are presented as mean ± SD unless otherwise noted.

*Unable to calculate *P* value.

[†]Decrease in ETco₂ less than or equal to 5 mm Hg (n = 10); increase or decrease in ETco₂ by less than 5 mm Hg (n = 25); increase in ETco₂ less than or equal to 5 mm Hg (n = 7).

[‡]Decrease in ETco₂ less than or equal to 5 mm Hg (n = 10); increase or decrease in ETco₂ by less than 5 mm Hg (n = 26); increase in ETco₂ less than or equal to 5 mm Hg (n = 8).

[§]Decrease in ETco₂ less than or equal to 5 mm Hg (n = 11); increase or decrease in ETco₂ by less than 5 mm Hg (n = 33); increase in ETco₂ less than or equal to 5 mm Hg (n = 7).

^{||}Decrease in ETco₂ less than or equal to 5 mm Hg (n = 11); increase or decrease in ETco₂ by less than 5 mm Hg (n = 33); increase in ETco₂ less than or equal to 5 mm Hg (n = 6).

[¶]Decrease in ETco₂ less than or equal to 5 mm Hg (n = 10); increase or decrease in ETco₂ by less than 5 mm Hg (n = 32); increase in ETco₂ less than or equal to 5 mm Hg (n = 7).

(12). ETco₂ has been studied in both chronic heart failure and PAH in relation to exercise (11, 13). In severe chronic heart failure and PAH, ETco₂ decreases during exercise (11, 13). That research group attributed declining ETco₂ in the setting of increasing exercise to an inability to increase pulmonary perfusion (11). Prior to these data, the relationship between ETco₂ and survival was not studied.

DL_{CO} measures the ability of a gas to transfer from the alveoli to red blood cells in the pulmonary capillaries. Because alveoli that are affected by dead space ventilation have no blood flow, they are unlikely to participate in absorbing gas into the alveolar capillaries. It would therefore follow that ETco₂ would correlate with DL_{CO} because both are markers of dead space ventilation. In performing

the Cox regression analysis, we found that the significant difference in survival between the group of patients with the higher ETco₂ and the group with lower ETco₂ was no longer present after adjustment for DL_{CO} in addition to age and sex. This suggests that DL_{CO} and ETco₂ offer some overlapping information. This observation is further supported by the correlation we found

Figure 4. End-tidal carbon dioxide pressure ($ETCO_2$) by functional class at enrollment. Data are presented as mean $\pm$ SD. $P = 0.61$ by Kruskal-Wallis test.

between DL_{CO} and $ETCO_2$. Many studies have demonstrated a reduction in DL_{CO} in patients with PAH and have shown that a reduced DL_{CO} is associated with a higher New York Heart Association functional class and is independently associated with death in these patients (14–16). Similar to DL_{CO} , $ETCO_2$ is not well correlated with invasive hemodynamics in a subset of patients,

but a shorter mean 6-minute walk distance was seen in nonsurvivors with $ETCO_2$ less than or equal to 29 mm Hg (17, 18). Although $ETCO_2$ and DL_{CO} may offer overlapping information, in contrast to DL_{CO} measurements, $ETCO_2$ measurements are quick, inexpensive, and may be obtained at the bedside without pulmonary function testing equipment.

Limitations

Our study is limited by the facts that it was a single-center study and that not every patient had a repeat $ETCO_2$ measurement. Other limitations include the relatively small number of patients with new initiation of therapy. Also, we did not measure arterial blood gases in our patients to exclude alveolar hyperventilation; however, patients did not have clinical evidence of metabolic acidosis that would reflect chronic compensation for hyperventilation. Additionally, $ETCO_2$ could be affected by congenital heart disease with significant shunt or significant parenchymal lung disease, so care must be taken when interpreting data for these patients.

Conclusions

Lower $ETCO_2$ is associated with increased risk of death in PAH. $ETCO_2$ is not changed significantly with oral PAH therapies. Further studies are needed to validate the prognostic utility of $ETCO_2$ in patients with PAH and to understand the relationship between DL_{CO} and $ETCO_2$. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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