Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Journal Club

Journal Club: Impaired Ventilatory Efficiency and Exercise Intolerance in Former/Current Smokers With Dyspnea Disproportionate to Their Lung Function: Pathophysiological Insights Gained Through Cardiopulmonary Exercise Testing

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Abbreviations: preserved ratio-impaired spirometry, **PRISm**; forced expiratory volume in 1 second, **FEV_1**; chronic obstructive pulmonary disease, **COPD**; minute ventilation, **VE**; carbon dioxide production, **VCO_2**; cardiopulmonary exercise testing, **CPET**; partial pressure of **CO_2**, **$PaCO_2$**; volume of oxygen consumed, **VO2peak**; diffusing capacity of the lungs for carbon monoxide, **DLCO**; Canadian study of Chronic Obstructive Lung Disease, **CanCOLD**; computed tomography, **CT**; modified Medical Research Council, **mMRC**; maximal oxygen consumption, **VO_{2max}**; COPD Assessment Test, **CAT**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; carbon monoxide transfer coefficient, **KCO**; ventilation/perfusion, **V/Q**

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Introduction

Many primary care and general pulmonologists see patients in clinic who are smokers or former smokers who report problems with exertional dyspnea and yet, when pulmonary function testing is performed, they demonstrate normal pulmonary function, and there are no significant radiographic abnormalities to explain their degree of dyspnea. Some patients will have a preserved ratio-impaired spirometry picture (PRISm) with a low forced expiratory volume in 1 second (FEV_1)[1-3] while others may have spirometry evidence of mild chronic obstructive pulmonary disease (COPD). Previous investigators have pointed to the importance of small airways disease[4-8] as perhaps the earliest evidence of cigarette smoke-related lung damage. One may consider and rule out alternative diagnoses that may be a cause for their dyspnea such as asthma and cardiovascular disease.[9-17] Other considerations may include inducible laryngeal obstruction or dysfunctional breathing disorder,[18-21] but ultimately, they are unable to explain to their patients what the cause of their shortness of breath is, even though their presumption is that they likely have "early Pre-COPD."[1,2]

Hence, there remains a keen interest in furthering our understanding of the underlying pathophysiological mechanisms for the not uncommon report of exertional dyspnea in smokers or former smokers with symptoms disproportionate to their lung function. Such individuals have been shown to have poor health status and increased mortality.[1-3] Indeed, further studies have indicated that the underlying pathophysiology of exertional dyspnea in this patient cohort goes beyond dynamic hyperinflation and may involve pulmonary

microvascular dysfunction.[12,14,17,22-26]

Other studies have examined the ventilatory efficiency-- (minute ventilation [VE] to carbon dioxide production [VCO_2]) VE/VCO_2 nadir: the lowest ventilatory rate able to remove 1 liter of CO_2 per minute during graded cardiopulmonary exercise testing (CPET).[27-31] While many clinicians are familiar with the concept of dynamic hyperinflation that can lead to breath stacking and dyspnea, fewer non-pulmonary physicians are familiar with the assessment of ventilatory efficiency.

Ventilatory efficiency essentially reflects the autonomic increase in ventilation in response to an increase in CO_2 production. CO_2 production is a result of bicarbonate neutralization of lactic acid that is produced by working muscles. Ventilatory efficiency is the amount of air ventilation (L/minute) required to exhale 1 liter of carbon dioxide produced. During cardiopulmonary exercise testing, a plot is made of ventilation as a function of the CO_2 production. This is referred to as the VE/VCO_2 slope. Accordingly, the slope will increase when the partial pressure of CO_2 ($PaCO_2$) is reduced by hyperventilation or when wasted ventilation or dead space is high. An increase in the slope is also observed in patients with chronic heart failure and in those with pulmonary hypertension.[32,33] A downward displacement of the slope occurs when the $PaCO_2$ setpoint is raised such as with primary alveolar hypoventilation.

Patients that have a high nadir require higher rates of ventilation to eliminate the CO_2 and this indicates impaired ventilatory efficiency. Abnormally high nadir VE/VCO_2 during exercise has been independently linked to dyspnea and low volume of oxygen consumed (VO_{2peak}) and mortality in COPD.[28,30,32,34,35] Correlations have been found between a high nadir VE/VCO_2 and lower resting diffusing capacity of the lungs for carbon monoxide (DLCO)[28,36] which is considered a surrogate marker of pulmonary vascular disease.

In this Journal Club we will focus on a recently published large population study that has shed light on the utility of performing CPET studies in patients with a history of cigarette smoking. The purpose of the study was to further understand the utility of assessing ventilatory efficiency nadir in smoking or former smoking individuals who report dyspnea that is disproportionately higher than what their pulmonary function testing and imaging studies would explain. Certainly, being able to identify a link between their smoking and evidence of lung microvascular damage may be helpful to encourage smokers to stop as they can appreciate that they are demonstrating signs that they are susceptible to the potential injurious effects of cigarette smoking. Hopefully, former smokers will be motivated not to restart as this identifies them as susceptible to the harmful effects of cigarette smoke in terms of COPD and other comorbidities such as cancer, diabetes, and cardiovascular and even kidney disease based on its effects on the vasculature. Further studies will be needed to address if this information leads to any pharmacological and non-pharmacologic interventions that might be able to reduce their dyspnea. The second study looks at the utility of inhaled nitric oxide as a selective pulmonary vascular vasodilator in improving exercise tolerance.

The third study looks at CPET and its ability to discriminate between dyspnea related to pulmonary vascular disease and heart failure. These papers offer an argument for perhaps considering CPET evaluation for these types of patients sooner rather than later.

Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.

Abstract 1
Impaired Ventilatory Efficiency, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease: Results from the CanCOLD Study

Phillips DB , Elbehairy AF, James MD, et al; CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network. *Am J Respir Crit Care Med.* 2022;205(12):1391-1402.
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Rationale: Impaired exercise ventilatory efficiency (high ventilatory requirements for CO_2 [VE/VCO_2]) provides an indication of pulmonary gas exchange abnormalities in chronic obstructive pulmonary disease(COPD).

Objectives: To determine 1) the association between high VE/VCO_2 and clinical outcomes (dyspnea and exercise capacity) and its relationship to lung function and structural radiographic abnormalities; and 2) its prevalence in a large population-based cohort.

Methods: Participants were recruited randomly from the population and underwent clinical evaluation, pulmonary function, cardiopulmonary exercise testing, and chest computed tomography. Impaired exercise ventilatory efficiency was defined by a nadir CO_2 above the upper limit of normal (ULN), using population-based normative values.

Measurements and Main Results: Participants included 445 never-smokers, 381 ever-smokers without airflow obstruction, 224 with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 COPD, and 200 with GOLD 2-4 COPD. Participants with VE/VCO_2 above the ULN were more likely to have activity-related dyspnea (Medical Research Council dyspnea scale ≥ 2; odds ratio [5-95% confidence intervals], 1.77 [1.31 to 2.39]) and abnormally low peak Vo2 (Vo2peak below the lower limit of normal; odds ratio, 4.58 [3.06 to 6.86]). The Kco had a stronger correlation with nadir VE/VCO_2 ($r = -0.38$; $P < 0.001$) than other relevant lung function and computed tomography metrics. The prevalence of VE/Vco2 above the ULN was 24% in COPD (similar in GOLD 1 and 2 through 4), which was greater than in never-smokers (13%) and ever-smokers (12%).

Conclusions: VE/VCO_2 above the ULN was associated with greater dyspnea and low VO_{2peak} and was present in 24% of all participants with COPD, regardless of GOLD stage. The results show the importance of recognizing impaired exercise ventilatory efficiency as a potential contributor to dyspnea and exercise limitation, even in mild COPD.

Comments

To date, the studies that have examined the utility of assessing ventilatory efficiency in the evaluation of COPD patients with dyspnea have been relatively few with small numbers of participants.[28,32,33,37-43] Phillips and colleagues from the Canadian Research Group Canadian study of Chronic Obstructive Lung Disease (CanCOLD) were well positioned to address this question. The consortium of 9 respiratory research centers in Canada has assembled a cross-sectional cohort of Canadians over 40 years old who have undergone a battery of tests including pulmonary function testing, exercise tolerance testing, computed tomography (CT) scanning, modified Medical Research Council (mMRC) breathlessness and COPD assessment test scoring.[44] The 1250 participants included smokers, former smokers, and never smokers who have been followed since 2010.

In this study, the authors focused on the evaluation of ventilatory efficiency during CPET. They assessed pulmonary gas exchange abnormalities, in terms of the prevalence and association of a high nadir ventilatory requirement for CO_2 (VE/VCO_2) and clinical outcomes including dyspnea, exercise capacity, and correlations to lung function and structural radiographic abnormalities. The authors utilized the assessment of nadir VE/VCO_2 (representing the lowest ventilation [L/minute] capable of removing 1 liter of carbon dioxide/minute to assess ventilatory efficiency). The nadir VE/VCO_2 was deemed to be above the upper limit of normal if it fell outside the values from a reference healthy population of older people.[23,45]

The group examined whether COPD individuals who had a high nadir VE/VCO_2 had greater breathlessness and worse exercise tolerance (low maximal oxygen consumption [VO_{2max}]) than the general population and whether there were certain lung function and imaging variables that closely correlated with the nadir VE/VCO_2. They also examined whether smokers without airflow obstruction differed in their nadir VE/VCO_2 compared to never smokers without airflow obstruction.

In the entire cohort the prevalence of impaired ventilatory efficiency was greater in the symptomatic participants (mMRC≥2 and/or COPD Assessment Test [CAT]≥10) when compared with the asymptomatic individuals (35% versus 9% $P<0.001$ respectively). Their results indicated that smoking individuals who had Global initiative for chronic Obstructive Lung Disease (GOLD)[46] defined airflow obstruction had significantly lower peak work rates compared to healthy never and ever smokers. Furthermore, the prevalence of abnormally high VE/VCO_2 was 24% in those individuals who had COPD and was similar across all GOLD stages however, those with the more severe (GOLD stages 2–4) airflow obstruction had the highest VE/VCO_2 nadir mark. In those individuals with GOLD 1 and 2–4, the presence or absence of comorbidities (cancer, diabetes, cardiovascular disease, or other respiratory disease) did not affect the prevalence of impaired ventilatory efficiency. They also found that the higher the nadir point, the greater the degree of dyspnea and the lower the peak oxygen consumption compared to those that had more efficient ventilation. They also showed that high nadir values were most strongly associated with the carbon monoxide transfer coefficient (KCO) and though statistically significant, the associations between high nadir values and

CT-based variables (emphysema burden, vascular volume abnormalities), were much weaker.

The authors offer that occult pulmonary vascular pathology could be the possible explanation for the individuals in whom the KCO was reduced. Other considerations suggested by the authors included occult cardiovascular disease and abnormal gas mixing with relatively preserved lung mechanics. The authors propose that the consistent association in the entire cohort between low KCO (and DLCO) and high nadir VE/VCO_2 implicates pulmonary microvascular dysfunction[22,24-26,47-49] as the primary pathogenic mechanism. The authors point out that past studies have shown that in GOLD stage 1 COPD, high nadir VE/VCO_2 is primarily influenced by elevated physiologic dead space reflecting abnormally high ventilation/perfusion (V/Q) (presumably secondary to reduced perfusion secondary to microvascular dysfunction) and to a lesser extent a low regulated level of arterial CO_2.[28,50,51] The CanCOLD investigators have conducted a comprehensive study to examine the role of cardiopulmonary exercise testing in the evaluation of this cohort of patients and the likely role that impaired ventilatory efficiency contributes to the observed dyspnea in patients with a history of smoking and preserved lung function. Hopefully, the identification of microvascular disease as the likely pathogenic mechanism will assist investigators in studying and/or developing novel therapeutic agents.

Abstract 2
Inhaled Nitric Oxide Improves Ventilatory Efficiency and Exercise Capacity in Patients With Mild COPD: A Randomized-Control Cross-Over Trial

Phillips DB, Brotto AR, Ross BA, et al; Canadian Respiratory Research Network. *J Physiol.* 2021;599(5):1665-1683. doi: https://doi.org/10.1113/JP280913

Key points: Patients with mild chronic obstructive pulmonary disease (COPD) have an elevated ventilatory equivalent to CO_2 production ($\dot{V}E / \dot{V}CO_2$) during exercise, secondary to increased dead space ventilation. The reason for the increased dead space is unclear, although pulmonary microvascular dysfunction and the corresponding capillary hypoperfusion is a potential mechanism. Despite emerging evidence that mild COPD is associated with pulmonary microvascular dysfunction, limited research has focused on experimentally modulating the pulmonary microvasculature during exercise in mild COPD. The present study sought to examine the effect of inhaled nitric oxide (iNO), a selective pulmonary vasodilator, on $\dot{V}E / \dot{V}CO_2$, dyspnoea and exercise capacity in patients with mild COPD. Experimental iNO increased peak oxygen uptake in mild COPD, secondary to reduced $\dot{V}E / \dot{V}CO2$ and dyspnoea. This is the first study to demonstrate that experimental manipulation of the pulmonary circulation alone, can positively impact dyspnoea and exercise capacity in mild COPD.

Abstract: Patients with mild chronic obstructive pulmonary disease (COPD) have an exaggerated ventilatory response to exercise, contributing to dyspnoea and exercise intolerance. Previous research in mild COPD has demonstrated an elevated ventilatory equivalent to CO_2 production ($\dot{V}E / \dot{V}CO_2$) during exercise, secondary to increased dead space ventilation. The reason for the increased dead space is unclear, although pulmonary microvascular dysfunction and the corresponding capillary hypoperfusion is a potential mechanism. The present study tested the hypothesis that inhaled nitric oxide (iNO), a selective pulmonary vasodilator, would lower $\dot{V}E / \dot{V}CO_2$ and dyspnoea, and improve exercise capacity in patients with mild COPD. In this multigroup randomized-control cross-over study, 15 patients with mild COPD (FEV_1 = 89 ± 11% predicted) and 15 healthy controls completed symptom-limited cardiopulmonary exercise tests while breathing normoxic gas or 40 ppm iNO. Compared with placebo, iNO significantly increased peak oxygen uptake (1.80 ± 0.14 vs. 1.53 ± 0.10 L·min-1 , P < 0.001) in COPD, whereas no effect was observed in controls. At an equivalent work rate of 60 W, iNO reduced $\dot{V}E / \dot{V}CO2$ by 3.8 ± 4.2 units (P = 0.002) and dyspnoea by 1.1 ± 1.2 Borg units (P < 0.001) in COPD, whereas no effect was observed in controls. Operating lung volumes and oxygen saturation were unaffected by iNO in both groups. iNO increased peak oxygen uptake in COPD, secondary to reduced $\dot{V}E / \dot{V}CO_2$ and dyspnoea. These data suggest that mild COPD patients demonstrate pulmonary microvascular dysfunction that contributes to increased $\dot{V}E / \dot{V}CO_2$, dyspnoea and exercise intolerance. This is the first study to demonstrate that experimental manipulation of the pulmonary circulation alone, can positively impact dyspnoea and exercise capacity in mild COPD

Comments

This elegant study from the same Canadian group has a very small number of participants. The group of patients in this study had mild COPD (FEV_1 89% but an abnormal FEV_1/FVC ratio). The rationale for presenting this paper is that inhaled nitric oxide improved exercise tolerance and reduced dyspnea scores compared to controls. These findings provide compelling evidence that the underlying pathophysiology for patients who demonstrate impaired ventilatory efficiency is related to pulmonary microvascular dysfunction. The results certainly support the hypothesis that the elevated dead space that appears to lead to a high nadir VE/VCO_2 may very well be a result of pulmonary microvasculature dysfunction, as the results were seen in the mild COPD participants but not in the control participants. This study provides insight that will undoubtedly lead to the development and/or study of potential therapeutic interventions such as selective pulmonary vasculature vasodilators.

Abstract 3
Exercise Ventilatory Inefficiency in Heart Failure and Chronic Obstructive Pulmonary Disease

Smith JR , Van Iterson EH , Johnson BD, Borlaug BA, Olson TP. *Int J Cardiol.* 2019;274:232-236.
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Background: Dyspnea on exertion is common to both heart failure (HF) and chronic obstructive pulmonary disease (COPD), and it is important to discriminate whether symptoms are caused by HF or COPD in clinical practice. The ventilatory equivalent for carbon dioxide (VE/VCO_2) slope and VE intercept (a reflection of pulmonary dead space) are two candidate non-invasive indices that could be used for this purpose. Thus, we compared non-invasive indexes of ventilatory efficiency in patients with HF and preserved or reduced ejection fraction (HFpEF and HFrEF, respectively) or COPD.

Methods: Patients with HFpEF (n = 21), HFrEF (n = 20), and COPD (n = 22) patients performed cardiopulmonary exercise testing to volitional fatigue. VE and gas exchange were measured via breath-by-breath open circuit spirometry. All data from rest to peak exercise were used to calculate VE/VCO_2 slope and VE intercept using linear regression. Receiver operating characteristic (ROC) curves were constructed to determine optimized cutoffs for VE/VCO_2 slope and VE intercept to discriminate HFpEF and HFrEF from COPD.

Results: HFrEF patients had a greater VE/VCO_2 slope than HFpEF and COPD patients (HFrEF: 40 ± 9; HFpEF: 32 ± 7; COPD: 32 ± 7) ($p < 0.01$). COPD patients had a greater VE intercept than HFpEF and HFrEF patients (COPD: 3.32 ± 1.66; HFpEF: 0.77 ± 1.23; HFrEF: 1.28 ± 1.19 L/min) ($p < 0.01$). A VE intercept of 2.64 L/min discriminated COPD from HF patients (AUC: 0.88, $p < 0.01$), while VE/VCO_2 slope did not ($p = 0.11$).

Conclusion: These findings demonstrate that VE intercept, not VE/VCO_2 slope, may discriminate COPD from both HFpEF and HFrEF patients.

Comments

Cardiovascular disease is a major comorbidity and cause of mortality for patients who have COPD. This study, while having a small number of participants, presents data that are quite interesting and suggest that CPET studies could potentially be very helpful with regard to teasing out the relative contributions of heart disease versus COPD for patients' reports of dyspnea symptoms. Such discrimination may be helpful for the group of patients who do not seem to improve with inhaled therapies or report ongoing symptoms despite noted improvement in lung function with inhaler therapy. Of course, studies must be performed with much larger numbers to confirm the validity of these results.

Bottom Line

It is not uncommon for primary care physicians and general pulmonologists to see patients who are current or former smokers who present with concerns around exertional dyspnea yet have little objective evidence of impairment on routine cardiac testing and/or pulmonary function tests and chest imaging studies. The work of the CanCOLD consortium of investigators and their longitudinal study cohort of participants have provided invaluable insights regarding many questions around natural history and underlying pathophysiology of patients who have COPD. The lead paper by Phillips and colleagues demonstrated the potential important role of damage to the pulmonary vasculature in patients with no or very mild airflow obstruction with

CPET evaluation demonstrating impaired ventilatory efficiency. The nitric oxide study by the same group is very compelling as to the role of pulmonary vascular dysfunction as a cause for the increased dead space, subsequent V/Q mismatch, and ventilatory inefficiency. The third study further highlights the ability to use CPET studies to look at ventilatory efficiency and the VE intercept to discern whether the patient's symptoms may be more a result of heart failure than lung disease. While CPET may seem to be quite an involved, invasive, and expensive test, the insights that one can glean from performing the test with regard to susceptibility to the effects of cigarette smoke and early evidence of injury can hopefully lead initially to preventive interventions and perhaps, ultimately, therapeutic interventions. Given the significant comorbidity of cardiovascular disease in smokers and COPD patients, CPET studies provide an integrative evaluation and perhaps should be thought of sooner rather than later for these types of patients.

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