Effect of Vaporized Cannabis on Exertional Breathlessness and Exercise Endurance in Advanced Chronic Obstructive Pulmonary Disease

A Randomized Controlled Trial

Sara J. Abdallah[1], Benjamin M. Smith[2,3,4,5,6,7,8], Mark A. Ware[9,10,11], Michelle Moore[1], Pei Zhi Li[3], Jean Bourbeau[2,3,4,5,6,7,8], and Dennis Jensen[1,2,3,4,5,7,8]

[1]Clinical Exercise and Respiratory Physiology Laboratory, Department of Kinesiology and Physical Education, and [2]Respiratory Division, Department of Medicine, McGill University, Montreal, Quebec, Canada; [3]Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University Health Centre, Montreal, Quebec, Canada; [4]Meakins-Christie Laboratories, Research Institute of the McGill University Health Centre (RI-MUHC), [5]McConnell Centre for Innovative Medicine, RI-MUHC, [6]Centre for Outcomes Research and Evaluation, RI-MUHC, and [7]Translational Research in Respiratory Diseases Program, RI-MUHC, Montreal, Quebec, Canada; [8]Research Centre for Physical Activity and Health, [9]Department of Family Medicine, and [10]Department of Anesthesia, McGill University, Montreal, Quebec, Canada; and [11]Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, Quebec, Canada

Abstract

Rationale: A series of studies conducted approximately 40 years ago demonstrated an acute bronchodilator effect of smoked cannabis in healthy adults and adults with asthma. However, the acute effects of vaporized cannabis on airway function in adults with advanced chronic obstructive pulmonary disease (COPD) remain unknown.

Objectives: To test the hypothesis that inhaled vaporized cannabis would alleviate exertional breathlessness and improve exercise endurance by enhancing static and dynamic airway function in COPD.

Methods: In a randomized controlled trial of 16 adults with advanced COPD (forced expiratory volume in 1 second [FEV_1], mean ± SD: 36 ± 11% predicted), we compared the acute effect of 35 mg of inhaled vaporized cannabis (18.2% Δ^9-tetrahydrocannabinol, <0.1% cannabidiol) versus 35 mg of a placebo control cannabis (CTRL; 0.33% Δ^9-tetrahydrocannabinol, <0.99% cannabidiol) on physiological and perceptual responses during cardiopulmonary cycle endurance exercise testing; spirometry and impulse oscillometry at rest; and cognitive function, psychoactivity, and mood.

Results: Compared with CTRL, cannabis had no effect on breathlessness intensity ratings during exercise at isotime (cannabis, 2.7 ± 1.2 Borg units vs. CTRL, 2.6 ± 1.3 Borg units); exercise endurance time (cannabis, 3.8 ± 1.9 min vs. CTRL, 4.2 ± 1.9 min); cardiac, metabolic, gas exchange, ventilatory, breathing pattern, and/or operating lung volume parameters at rest and during exercise; spirometry and impulse oscillometry–derived pulmonary function test parameters at rest; and cognitive function, psychoactivity, and mood.

Conclusions: Single-dose inhalation of vaporized cannabis had no clinically meaningful positive or negative effect on airway function, exertional breathlessness, and exercise endurance in adults with advanced COPD.

Clinical trial registered with www.clinicaltrials.gov (NCT03060993).

Keywords: dyspnea; functional capacity; marijuana; chronic obstructive pulmonary disease

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Correspondence and requests for reprints should be addressed to Sara J. Abdallah, M.Sc., Department of Kinesiology and Physical Education, 475 Pine Avenue West, Montreal, QC, H2W 1S4 Canada. E-mail: sara.j.abdallah@gmail.com.

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In adults with chronic obstructive pulmonary disease (COPD), pathophysiological abnormalities in static and dynamic airway function (e.g., hyperinflation) are mechanistically linked to breathlessness and exercise intolerance (1, 2), which are independently associated with increased morbidity and mortality (3, 4). Despite intensive management of their underlying pulmonary pathophysiology with inhaled bronchodilators and antiinflammatory agents, 46–91% of adults with advanced COPD suffer from persistent and disabling breathlessness at rest and on minimal exertion (5–8). Therefore, it is important to identify adjunct therapies to help alleviate breathlessness and improve exercise tolerance in advanced COPD.

Amid widespread changes in the regulatory landscape of recreational and medicinal use of cannabis, there has been growing interest in understanding the therapeutic potential of its main cannabinoid constituent, Δ^9-tetrahydrocannabinol (THC) (9), which provides symptomatic relief of acute and chronic pain across a range of malignant and nonmalignant diagnoses (10).

Mechanistically, THC exerts its effects by binding to cannabinoid type 1 (CB_1) and to a lesser extent type 2 (CB_2) receptors, which are differentially expressed in the central and peripheral nervous systems as well as in some peripheral tissues, including the lungs (11, 12). Grassin-Delyle and colleagues (13) demonstrated that THC induced a concentration-dependent inhibition of cholinergic contraction in human airway smooth cells via activation of prejunctional CB_1 receptors. In keeping with these observations, Vachon and colleagues (14) and Tashkin and colleagues (15–18) demonstrated an acute bronchodilator effect of smoked cannabis (~500 mg of 1–2% THC) in healthy adults and adults with asthma that was comparable in magnitude and duration of effect to the β_2-adrenergic receptor agonist isoproterenol. Although no study has evaluated the bronchodilator and therapeutic potential of inhaled cannabis in COPD, a large cross-sectional study of adults with COPD reported a positive association between cannabis use and forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), even after adjusting for cigarette smoking history (19). Together, these studies suggest that the endocannabinoid system may represent a novel therapeutic target to enhance static and dynamic airway function, with attendant improvements in exertional breathlessness and exercise tolerance in advanced COPD.

The aim of this randomized controlled trial was to evaluate the acute effect of inhaled vaporized cannabis versus a placebo control (CTRL) on exertional breathlessness

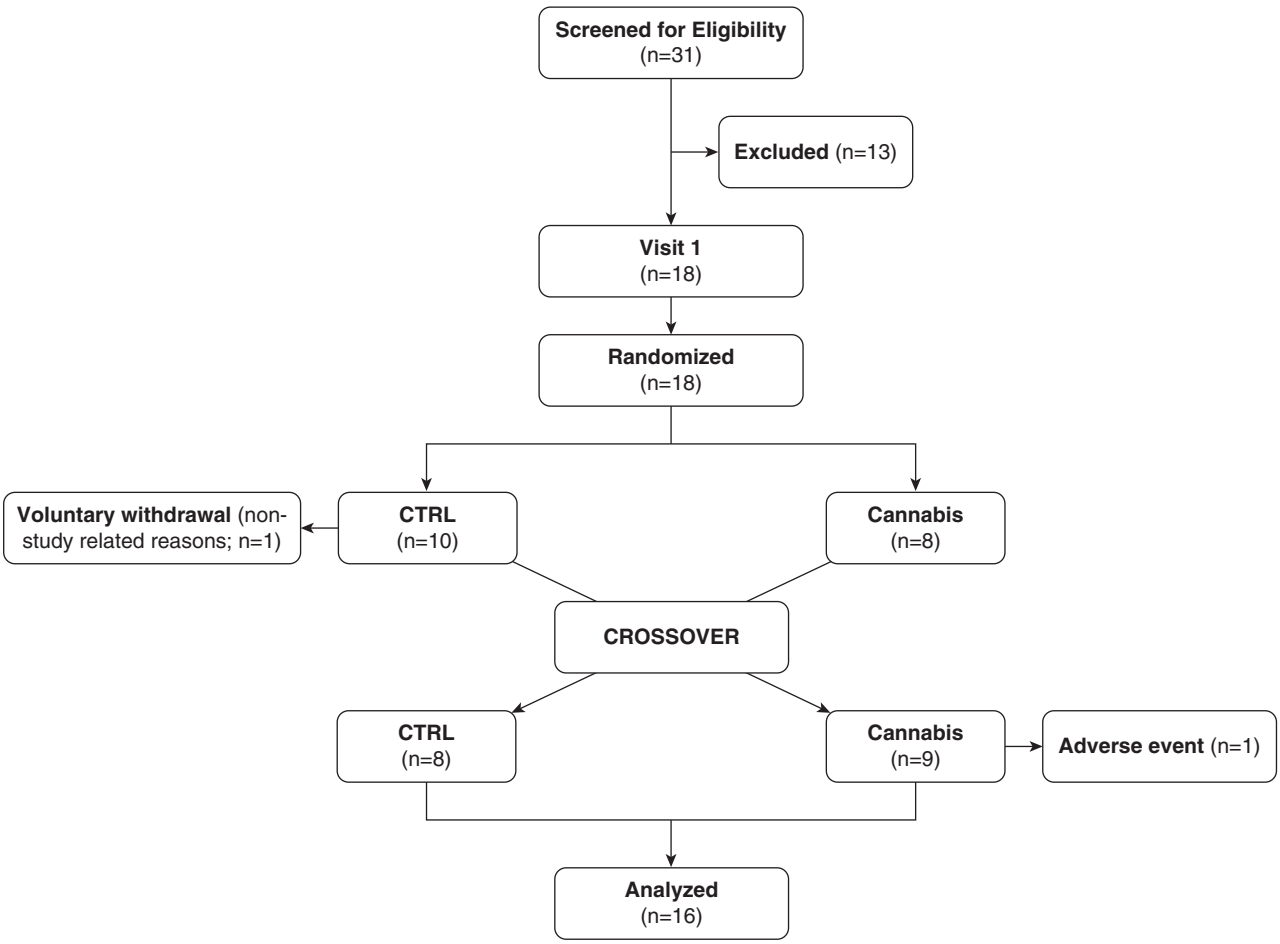

Figure 1. CONSORT diagram of the study population. CONSORT = Consolidated Standards of Reporting Trials; CTRL = placebo control cannabis.

and exercise endurance in symptomatic adults with advanced COPD. We hypothesized that single-dose inhalation of vaporized cannabis versus CTRL would alleviate exertional breathlessness and improve exercise endurance by enhancing static and dynamic airway function.

Methods

Study Design

This single-center, randomized, double-blind, crossover trial (ClinicalTrials.gov; NCT03060993) consisted of two intervention periods separated by a washout period of at least 5 days. The study protocol and informed consent form received regulatory approval from Health Canada (Control No. 202091) and ethics approval from the Research Institute of the McGill University Health Centre (COPD-THC/2017-2614). The study took place at the McConnell Centre for Innovative Medicine of the McGill University Health Centre, and participants were recruited from the Montreal Chest Institute (Montreal, QC, Canada).

After providing written and informed consent, participants completed a screening/familiarization visit followed by two randomly assigned treatment visits. Visit 1 included: evaluation of participant-reported breathlessness (20, 21), health status (22), and anxiety/depression (23); post-bronchodilator pulmonary function testing; and a symptom-limited incremental cardiopulmonary cycle exercise test (CPET) to determine peak power output, defined as the highest power output that the participant was able to sustain for at least 30 seconds. Before the administration of cannabis or CTRL at Visits 2 and 3, a urine sample was collected for toxicology screening of THC; cognitive function (24), psychoactivity, and mood (25) were assessed; and spirometry and impulse oscillometry (iOS) were performed. Participants then inhaled vaporized cannabis or CTRL. Two minutes thereafter, participants completed tests of cognitive function (24), psychoactivity, and mood (25) followed immediately by spirometry, iOS, and a symptom-limited constant-load cycle CPET at 75% of peak power output. Intravenous blood samples for measurement of plasma concentrations of THC and its metabolites and of cannabidiol (CBD) were obtained before and 2, 30, 75, and 180 minutes after inhalation of cannabis and CTRL. *See* the online supplement for details on study design.

Participants

Participants included men and women (age, ⩾40 yr) with Global Initiative for Obstructive Lung Disease stage 3 or 4 COPD (26). *See* the online supplement for details on eligibility criteria.

Intervention

Participants received 35 mg of cannabis (Tilray House Blend-active [THC, 18.2%; CBD, <0.1%]; Tilray) or 35 mg of CTRL (Tilray House Blend-control [THC, 0.33%; CBD, 0.99%]) administered with a Volcano Digit vaporizer (Storz & Bickel America, Inc.).

Procedures

Dried plant cannabis and CTRL material were dispensed into the Volcano Digit filling chamber by the McGill University Health Centre's research pharmacist. The filling chamber was placed in the vaporizer at a heating temperature and filling time of 190°C and 30 seconds, respectively. Approximately 5.5 L of the vaporized compounds was collected in a balloon fitted with a mouthpiece and a one-way valve (Storz & Bickel America, Inc.), allowing the vapor to remain in the balloon until inhalation. Participants inhaled the entire contents of the balloon using the Foltin puff procedure (27). Briefly, participants were instructed to "hold the balloon with one hand and put the mouthpiece in

Table 1. Baseline participant characteristics

Parameter	Value*
Male:Female, No.	10:6
Age, yr	65.4 ± 7.7 (66; 47 to 77)
Height, cm	165.6 ± 7.3 (168; 150 to 175)
Body mass, kg	70.9 ± 11.7 (72; 50 to 89)
Body mass index, $kg \cdot m^{-2}$	25.8 ± 11.8 (26.7; 18.6 to 33.5)
Cigarette smoking history, pack-years	63 ± 28 (60; 21 to 127)
Cannabis smoking history, joint-years	34 ± 99 (0; 0 to 392)
Post-bronchodilator pulmonary function	
FEV_1, L (% predicted)	0.88 ± 0.28 (36 ± 11) (0.98; 0.51 to 1.53)
FEV_1/FVC, %	31 ± 7 (31; 20 to 47)
TLC, L (% predicted)	8.10 ± 2.08 (143 ± 42) (7.86; 5.81 to 13.56)
RV, L (% predicted)	5.04 ± 2.51 (242 ± 123) (4.41; 2.31 to 11.64)
FRC, L (% predicted)	6.40 ± 2.17 (210 ± 78) (5.85; 4.24 to 12.32)
IC, L (% predicted)	1.70 ± 0.43 (64 ± 13) (1.79; 0.92 to 2.24)
D_{LCO}, $ml \cdot min^{-1} \cdot mm\ Hg^{-2}$ (% predicted)	11.9 ± 3.9 (62 ± 4) (11.7; 4.0 to 18.8)
sRaw, $cm\ H_2O \cdot L^{-1} \cdot s^{-2}$ (% predicted)	40.4 ± 17.3 (900 ± 478) (34.9; 20.5 to 78.7)
Impulse oscillometry	
R_5, $kPa \cdot L^{-1} \cdot s$	0.51 ± 0.13 (0.49; 0.27 to 0.82)
R_{20}, $kPa \cdot L^{-1} \cdot s$	0.32 ± 0.07 (0.32; 0.24 to 0.50)
X_5, $kPa \cdot L^{-1} \cdot s$	−0.28 ± 0.12 (−0.27; −0.55 to −0.76)
F_{res}, $1 \cdot s^{-1}$	22.83 ± 3.49 (22.43; 17.73 to 28.06)
A_X, $kPa \cdot L^{-1}$	2.29 ± 1.11 (2.14; 1.1 to 4.8)
Breathlessness and health status	
mMRC score, 0–4	2.8 ± 0.5 (3; 2 to 3)
BDI focal score, out of 12	4.1 ± 1.8 (3; 1 to 7)
Oxygen cost diagram, % full scale	44 ± 17 (38; 23 to 81)
CAT score, out of 40	15.7 ± 7.8 (16; 4 to 28)
HADS score, out of 42	12.3 ± 8.1 (13; 0 to 31)
COPD medication summary	
LABA + LAMA, No.	7
LABA + LAMA + ICS, No.	9

Definition of abbreviations: A_X = area of reactance; BDI = Baseline Dyspnea Index; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; F_{res} = resonant frequency; FEV_1 = forced expiratory volume in 1 second; FRC = functional residual capacity; FVC = forced vital capacity; HADS = Hospital Anxiety and Depression Scale; IC = inspiratory capacity; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council Dyspnoea Scale; R_5 and R_{20} = resistance at 5 and 20 Hz, respectively; RV = residual volume; sRaw = specific airway resistance; TLC = total lung capacity; X_5 = reactance at 5 Hz.
*Values represent means ± SD (median; range). Cannabis smoking history was calculated as number of joints per day × number of years smoking.

your mouth," "inhale for 5 seconds," "hold vapor in your lungs for 10 seconds," "exhale and wait for 40 seconds before repeating puff cycle." Spirometry and iOS were performed with automated equipment and according to recommended techniques (28–31). Exercise tests were conducted on an electronically braked cycle ergometer, using a computerized CPET system: cardiac, metabolic, gas exchange, breathing pattern, and operating lung volume parameters were collected and analyzed as previously described (32, 33). Using Borg's modified 0–10 category ratio scale (34), participants rated the intensity and unpleasantness of their breathlessness, as well as the intensity of their leg discomfort at rest, every 2 minutes during CPET, and at end-exercise. Each participant's blinded treatment preference was assessed at the end of Visit 3. *See* the online supplement for details on experimental procedures.

Outcome Variables

The primary outcome was the post-treatment difference in breathlessness intensity ratings during exercise at isotime, defined as the highest equivalent 2-minute interval of exercise completed by a given participant during each of the constant-load CPETs. The coprimary outcome was the post-treatment difference in exercise endurance time (EET), defined as the duration of loaded pedaling during constant-load CPET. The constant-load cycle CPET was selected over other exercise test modalities (e.g., endurance shuttle walking test), as it is generally regarded as the most responsive exercise testing modality in the evaluation of interventional efficacy in COPD, particularly as it relates to exertional breathlessness and EET (35). *See* the online supplement for details on secondary outcome variables.

Sample Size

Using a two-tailed paired-subject formula with $\alpha = 0.05$, $\beta = 0.80$, and an expected effect size of 0.80 (36), we estimated that at least 15 participants were needed to detect a minimal clinically important difference (MCID) of ±1 Borg unit in breathlessness intensity during exercise at isotime (37) and of ±101 seconds in EET (38) after inhalation of vaporized cannabis versus CTRL.

Randomization

Participants were randomized at a 1:1 ratio according to a computer-generated block randomization schedule (block size, 4) prepared by a third-party statistician not involved in the trial. Participants and investigators were blinded to the randomization schedule.

Statistical Methods

Participants who completed both cannabis and CTRL arms of the trial were included in the analysis. Linear mixed-models regression with random intercepts was used to analyze post-treatment differences in EET as well as in all physiological and perceptual responses to constant-load CPET, accounting for period and sequence effects. Data were analyzed with the SAS statistical package, version 9.4 (SAS Institute Inc.) and SigmaStat, version 3.5 (Systat Software Inc.). Statistical significance was set at $P < 0.05$, and values are reported as means ± SD unless stated otherwise. *See* the online supplement for additional information on the statistical analyses performed.

Results

Eighteen of 31 participants assessed for eligibility were randomized (Figure 1). One of these 18 participants voluntarily withdrew between Visits 1 and 2, and another participant was excluded after an adverse event (*see below*). Baseline characteristics of the 16 participants who completed the trial are presented in Tables 1 and 2. Twelve of the 16 participants had a self-reported cannabis smoking history of less than one joint in their lifetime. The other four participants had a mean ± SD self-reported cannabis smoking history of 34 ± 99 joint-years (range, 1.4–392). *See* the online supplement for additional information on participant characteristics.

Primary Outcomes

Compared with CTRL, cannabis had no effect on breathlessness intensity ratings at isotime or on EET (Table 3 and Figure 2). There was no period or sequence effect on our primary outcomes. Four participants had a cannabis-induced decrease in breathlessness intensity ratings at isotime by the MCID of at least 1 Borg unit (responders) compared with the remaining 12 participants who did not (nonresponders) (Figures 2D and 2G). Two participants had a cannabis-induced increase in EET by the MCID of at least 101 seconds compared with the remaining 14 participants who did not (Figures 2F and

Table 2. Physiological and perceptual responses at symptom-limited peak of incremental cycle exercise testing in adults with advanced chronic obstructive pulmonary disease

Parameter	Value*
$\dot{V}_{O_2}$, ml · kg · min^{-1} (% predicted)	10.9 ± 2.9 (48 ± 13)
HR, beats · min^{-1} (% predicted)	117 ± 13 (67 ± 13)
Breathlessness intensity, Borg 0–10 units	5.2 ± 2.2
Breathlessness unpleasantness, Borg 0–10 units	5.4 ± 2.6
Leg discomfort, Borg 0–10 units	4.7 ± 1.9
$\dot{V}_E$, L · min^{-1} (% estimated MVV)	29.4 ± 10.5 (96 ± 23)
V_T, L	1.06 ± 0.29
f, breaths · min^{-1}	27.9 ± 7.2
ΔIC from rest, L	−0.67 ± 0.40
IRV, L	0.36 ± 0.20
$\dot{V}_E/\dot{V}_{CO_2}$	38.1 ± 5.7
$P_{ET_{CO_2}}$, mm Hg	41.8 ± 15.9
Sp_{O_2}, %	93 ± 3
ΔSp_{O_2} from rest, %	−2.2 ± 1.4
Reasons for stopping exercise	
Breathlessness, No.	6
Leg discomfort, No.	2
Breathlessness and leg discomfort, No.	7
Other, No.	1

Definition of abbreviations: Δ = exercise-induced change; f = breathing frequency; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; MVV = maximal voluntary ventilation (estimated as $FEV_1 \times 35$); $P_{ET_{CO_2}}$ = partial pressure of end-tidal carbon dioxide; Sp_{O_2} = oxygen saturation by pulse oximetry; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalent for carbon dioxide; $\dot{V}_{O_2}$ = rate of oxygen uptake; V_T = tidal volume.
*Values represent means ± SD.

Table 3. Effect of inhaled vaporized cannabis versus control on physiological and perceptual responses at rest, at a standardized submaximal time (isotime) during constant-load cycle exercise testing, and at symptom-limited peak of constant-load cycle exercise testing in adults with advanced chronic obstructive pulmonary disease*

	Rest		Isotime		Peak	
	Control	Cannabis	Control	Cannabis	Control	Cannabis
Cycle exercise time, min	—	—	2.4 ± 0.8	2.4 ± 0.8	4.2 ± 1.9	3.8 ± 1.9
Breathlessness intensity, Borg 0–10 units	0.4 ± 0.4	0.7 ± 1.1	2.6 ± 1.3	2.7 ± 1.2	5.1 ± 1.8	5.4 ± 2.0
Breathlessness unpleasantness, Borg 0–10 units	0.5 ± 0.8	0.5 ± 1.0	2.6 ± 1.2	2.8 ± 1.8	5.3 ± 2.2	5.1 ± 2.4
Leg discomfort, Borg 0–10 units	0.4 ± 0.6	0.7 ± 1.0	2.4 ± 1.7	2.9 ± 1.9	4.6 ± 2.4	4.4 ± 2.6
$\dot{V}O_2$, ml · kg · min^{-1}	4.0 ± 0.6	4.3 ± 0.8	9.8 ± 2.2	9.8 ± 2.5	11.3 ± 2.1	11.0 ± 2.9
$\dot{V}CO_2$, ml · kg · min^{-1}	3.7 ± 0.5	4.0 ± 0.8	9.5 ± 3.3	9.8 ± 3.5	11.6 ± 3.0	11.3 ± 3.8
HR, beats · min^{-1}	84 ± 12	86 ± 12	104 ± 12	107 ± 14	112 ± 13	114 ± 18
O_2 pulse, ml O_2 · beat^{-1}	3.4 ± 0.5	4.0 ± 2.3	6.7 ± 1.6	7.4 ± 4.5	7.1 ± 1.6	7.7 ± 4.4
$\dot{V}E$, L · min^{-1}	13.4 ± 2.7	14.3 ± 3.4	26.1 ± 10.1	26.4 ± 8.9	29.5 ± 9.6	29.6 ± 10.0
V_T, L	0.81 ± 0.24	0.77 ± 0.16	1.05 ± 0.26	1.07 ± 0.29	1.11 ± 0.28	1.08 ± 0.30
f, breaths · min^{-1}	17.9 ± 6.4	19.6 ± 6.0	25.6 ± 7.4	25.6 ± 7.2	26.8 ± 5.7	27.9 ± 6.7
IC, L	2.08 ± 0.51	2.04 ± 0.60	1.54 ± 0.40	1.48 ± 0.41	1.44 ± 0.44	1.41 ± 0.44
ΔIC from rest, L	—	—	−0.54 ± 0.34	−0.56 ± 0.28	−0.65 ± 0.34	−0.63 ± 0.38
IRV, L	1.27 ± 0.40	1.27 ± 0.46	0.49 ± 0.29	0.41 ± 0.26	0.32 ± 0.24	0.33 ± 0.23
$\dot{V}E/\dot{V}CO_2$	51.7 ± 6.1	51.6 ± 5.7	39.0 ± 5.0	38.9 ± 4.5	36.2 ± 5.3	37.2 ± 5.1
$P_{ET}CO_2$, mm Hg	32.8 ± 3.2	33.1 ± 3.2	37.2 ± 5.0	37.4 ± 4.3	39.0 ± 5.9	38.4 ± 5.3
Sp_{O_2}, %	94 ± 5	96 ± 2	93 ± 3	93 ± 3	92 ± 4	93 ± 3
Reasons for stopping exercise						
Breathlessness, No. (% contribution)	—	—	—	—	8 (62 ± 34)	7 (61 ± 33)
Leg discomfort, No. (% contribution)	—	—	—	—	2 (27 ± 28)	3 (13 ± 29)
Breathlessness and leg discomfort, No.	—	—	—	—	4	4
Other, No.	—	—	—	—	2	2

Definition of abbreviations: Δ = exercise-induced change; f = breathing frequency; HR = heart rate; IC = inspiratory capacity; IRV = inspiratory reserve volume; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; Sp_{O_2} = oxygen saturation by pulse oximetry; $\dot{V}E$ = minute ventilation; $\dot{V}CO_2$ = rate of carbon dioxide production; $\dot{V}E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ = rate of oxygen uptake; V_T = tidal volume.
*Values represent means ± SD.

2I). A significant negative correlation was observed between cannabis-induced changes in breathlessness intensity ratings at isotime and in EET (Figure 3).

Secondary Outcomes

Pulmonary function. Compared with CTRL, cannabis had no effect on spirometry and iOS-derived pulmonary function parameters at rest (Table 4 and Figure E2).

Physiological and perceptual responses to exercise. Compared with CTRL, cannabis had no effect on cardiac, metabolic, gas exchange, ventilatory, breathing pattern, operating lung volume, breathlessness unpleasantness, and leg discomfort responses at rest or during exercise (Figures 2–5 and Table 3). The locus of symptom limitation (Table 3), the relative contributions of breathlessness and leg discomfort to exercise cessation (Table 3), and the selection frequency of breathlessness descriptors at end-exercise (*see* Figure E1 in the online supplement) were not different after inhalation of cannabis versus CTRL. *See* the online supplement for details on participants' blinded treatment preference.

Blood biochemistry. Plasma THC levels were approximately 17 and 44 times higher after inhalation of cannabis versus CTRL at the 2- and 30-minute post-treatment time periods, respectively. Plasma 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) levels were approximately 16 times higher after inhalation of cannabis versus CTRL at each of the 2-, 30-, 75-, and 180-minute post-treatment time periods (Table 5). Peak plasma THC, *trans*-Δ^9-tetrahydrocannabinol-9-acid A (THCA), and 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) levels during the cannabis condition, and of THC and CBD during the CTRL condition, were achieved 2 minutes post-treatment. Peak plasma THC-COOH levels were achieved 30 minutes after cannabis and CTRL conditions (Table 5 and Figure 6). Compared with the pretreatment condition, inhaled cannabis increased plasma THCA and 11-OH-THC levels at 2, 30, and 75 minutes post-treatment, whereas inhaled CTRL had no effect (Table 5). Compared with the pretreatment condition, inhaled CTRL increased plasma CBD levels at 2, 30, and 75 minutes post-treatment, whereas inhaled cannabis had no effect (Table 5).

Cannabis-related side effects and adverse events. None of the participants coughed after inhalation of CTRL. By contrast, six participants coughed after inhalation of cannabis, with five of these six participants reporting clinically significant worsening of exertional breathlessness at isotime by at least 1 Borg unit (Figures 2G and 3).

Measures of cognitive function, psychoactivity, and mood were not significantly different after inhalation of vaporized cannabis versus CTRL (Table 6 and Figures E3 and E4). Compared with the pretreatment condition, inhalation of cannabis was associated with modest and statistically significant decreases in ratings of anxiety and increases in ratings of feeling drunk, feeling stoned, feeling high, experiencing good drug effects, experiencing

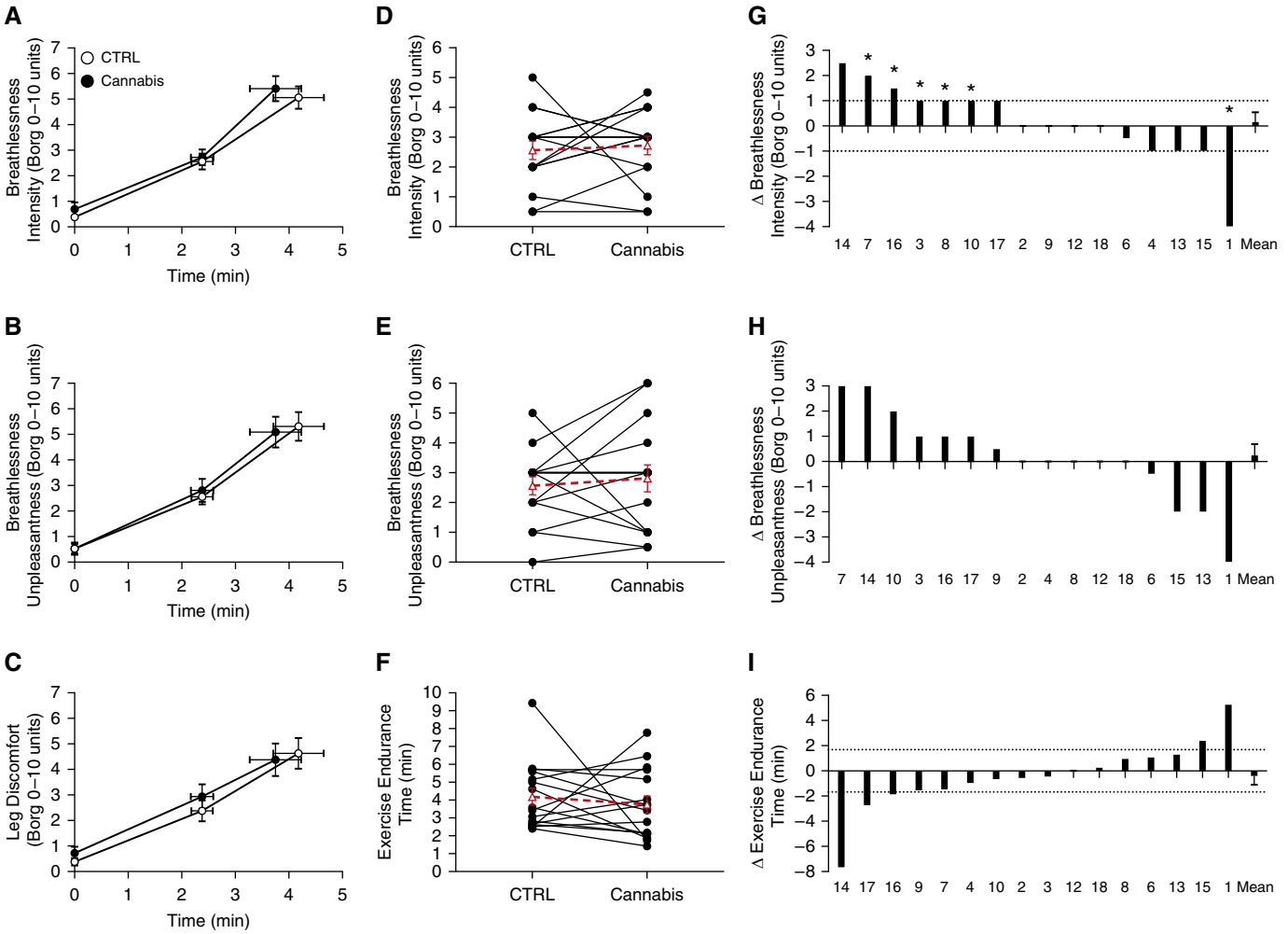

Figure 2. Effect of inhaled vaporized cannabis versus control (CTRL) on exertional breathlessness and exercise endurance in adults with advanced chronic obstructive pulmonary disease. (*A*) Mean ± SEM breathlessness intensity ratings, (*B*) breathlessness unpleasantness ratings, and (*C*) intensity ratings of leg discomfort at rest and during symptom-limited constant-load cycle exercise testing at 75% of peak incremental power output. (*D* and *G*) Individual participant post-treatment values and post-treatment differences in breathlessness intensity ratings during exercise at isotime, (*E* and *H*) breathlessness unpleasantness ratings during exercise at isotime, and (*F* and *I*) exercise endurance time, where red symbols with dashed horizontal lines in panels *D–F* denote means ± SEM. Dashed horizontal lines in panels *G* and *I* denote minimally clinically important differences for breathlessness intensity (37) and exercise endurance time (38). Δ = post-treatment difference (cannabis − CTRL). *Participants who coughed after inhalation of vaporized cannabis.

bad drug effects, and liking the drug effects. In contrast, psychoactivity and mood ratings were not different before versus after inhalation of CTRL.

A participant experienced vasovagal syncope during the 2-minute venous blood-sampling period of the cannabis visit. After a few hours of rest while under medical observation, the participant was permitted to go home. Both the study physician and data safety committee determined that this adverse event was most likely due to the blood-sampling procedure itself and not inhalation of cannabis.

Discussion

This randomized controlled trial is the first to demonstrate that single-dose inhalation of vaporized cannabis versus CTRL had no effect on exertional breathlessness, exercise endurance, and airway function in symptomatic adults with advanced COPD receiving dual- or triple-inhalation therapy for management of their underlying pulmonary pathophysiology.

We administered 35 mg of dried herbal cannabis containing 18.2% THC, a dose comparable to that used in earlier studies by Vachon and colleagues (14) and Tashkin and colleagues (15–18) wherein smoked, aerosolized, and orally administered THC induced bronchodilation in adults with and without asthma. Despite using a similar dose, inhaled vaporized cannabis did not enhance static and dynamic airway function in our participants with advanced COPD.

We offer the following explanations for the lack of effect of inhaled vaporized cannabis versus CTRL on airway function and, by extension, exertional breathlessness and EET in our trial. First, previous

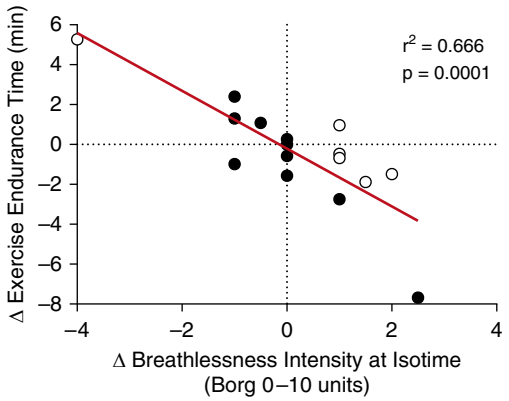

Figure 3. Relationship between post-treatment differences in breathlessness intensity ratings during exercise at isotime and exercise endurance time in adults with advanced chronic obstructive pulmonary disease. Open circles denote participants who coughed after inhalation of vaporized cannabis. Δ = post-treatment difference (cannabis − control).

studies reporting bronchodilation after administration of smoked cannabis used "blended natural marijuana" assayed at 1% or 2% THC (16–18). It is unclear if these cannabis preparations were devoid of other cannabinoids (e.g., CBD, cannabinol) that may have had a direct bronchodilator effect and/or facilitated the bronchodilator effect of THC. However, this is unlikely as large doses (up to 1,200 mg) of orally administered CBD and cannabinol, in the absence of THC, did not induce bronchodilation in healthy men when compared with placebo (39). Second, previous studies that have demonstrated a bronchodilator effect of smoked cannabis used a uniform smoking procedure that consisted of "smoking deeply" over 2–4 seconds followed by a 15-second breathhold (16–18). To standardize drug delivery we utilized the Foltin puff procedure, where participants were instructed to inhale the vaporized cannabis for 5 seconds and to hold the vapor in their lungs for 10 seconds. It is possible that relatively shallower inhalations and shorter breathholding times used in our trial might have diminished the potential positive effects of inhaled THC on static and dynamic airway function in our participants. Third, adults with COPD have abnormal airway geometry and fewer terminal bronchioles compared with their healthy counterparts (40–42). Therefore, limited delivery of vaporized THC into the airways and lungs of our participants may explain our null results. Structural abnormalities of the tracheobronchial tree in our participants may also account for the lower observed peak plasma THC levels of approximately 14 ng/ml versus approximately 45 ng/ml reported by Ware and colleagues (43) in adults with neuropathic pain after single-dose inhalation (smoked) of a comparatively low dose of 25 mg of dried herbal cannabis containing 9.4% THC. Our relatively low peak plasma THC levels may also reflect the vaporization temperature of 190°C used in this trial. Pomahacova and colleagues (44) reported that vaporizing dried herbal cannabis at 230°C versus 185°C produced a vapor with a threefold higher yield of THC. Finally, all of our participants were receiving inhaled dual or triple therapy for management of their COPD, while six participants used their short-acting inhaled β_2-agonist (SABA) bronchodilator 3.5 ± 1.7 and 4.2 ± 1.3 hours before Visits 2 and 3, respectively. It is unlikely that the SABA used by six of our 16 participants significantly altered the effect of inhaled vaporized cannabis airway physiology, breathlessness, and EET, particularly as the duration of efficacy of the SABA is 3–4 hours. Indeed, we found no significant effect of inhaled vaporized cannabis versus CTRL on spirometry and iOS-derived pulmonary function parameters at rest in participants with COPD who used their SABA versus those who did not (data not shown).

We observed a negative correlation between the cannabis-induced change in exertional breathlessness intensity ratings at isotime and EET. We identified four cannabis responders (participants with cannabis-induced relief of exertional breathlessness at isotime by the MCID of ⩾1 Borg unit) and 12 nonresponders.

Table 4. Effect of inhaled vaporized cannabis versus control on spirometry and impulse oscillometry–derived pulmonary function test parameters at rest in adults with advanced chronic obstructive pulmonary disease*

	Control		Cannabis	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Spirometry				
FVC, L	2.87 ± 0.91	2.93 ± 0.85	2.94 ± 0.91	2.90 ± 0.90
FEV_1, L	0.89 ± 0.26	0.89 ± 0.26	0.89 ± 0.25	0.89 ± 0.24
FEV_1/FVC, %	32 ± 8	31 ± 7	32 ± 9	32 ± 6
$FEF_{25–75\%}$, $L \cdot s^{-1}$	0.26 ± 0.06	0.26 ± 0.07	0.26 ± 0.07	0.26 ± 0.07
PEF, $L \cdot s^{-1}$	2.81 ± 0.82	2.59 ± 0.87	2.60 ± 0.78	2.62 ± 0.84
Impulse oscillometry				
R_5, $kPa \cdot L^{-1} \cdot s$	0.60 ± 0.18	0.59 ± 0.24	0.60 ± 0.14	0.58 ± 0.17
R_{20}, $kPa \cdot L^{-1} \cdot s$	0.34 ± 0.08	0.34 ± 0.13	0.34 ± 0.05	0.33 ± 0.06
X_5, $kPa \cdot L^{-1} \cdot s$	−0.35 ± 0.15	−0.34 ± 0.16	−0.35 ± 0.15	−0.34 ± 0.16
F_{res}, $1 \cdot s^{-1}$	23.9 ± 4.1	24.0 ± 5.1	22.6 ± 3.7	23.3 ± 4.2
A_X, $kPa \cdot L^{-1}$	3.04 ± 1.76	3.04 ± 1.99	2.85 ± 1.55	2.88 ± 1.81

Definition of abbreviations: A_X = area of reactance; $FEF_{25–75\%}$ = forced expiratory flow at 25–75% of the FVC maneuver; FEV_1 = forced expiratory volume in 1 second; F_{res} = resonant frequency; FVC = forced vital capacity; PEF = peak expiratory flow; R_5 and R_{20} = resistance at 5 and 20 Hz, respectively; X_5 = reactance at 5 Hz.
*Values represent means ± SD.

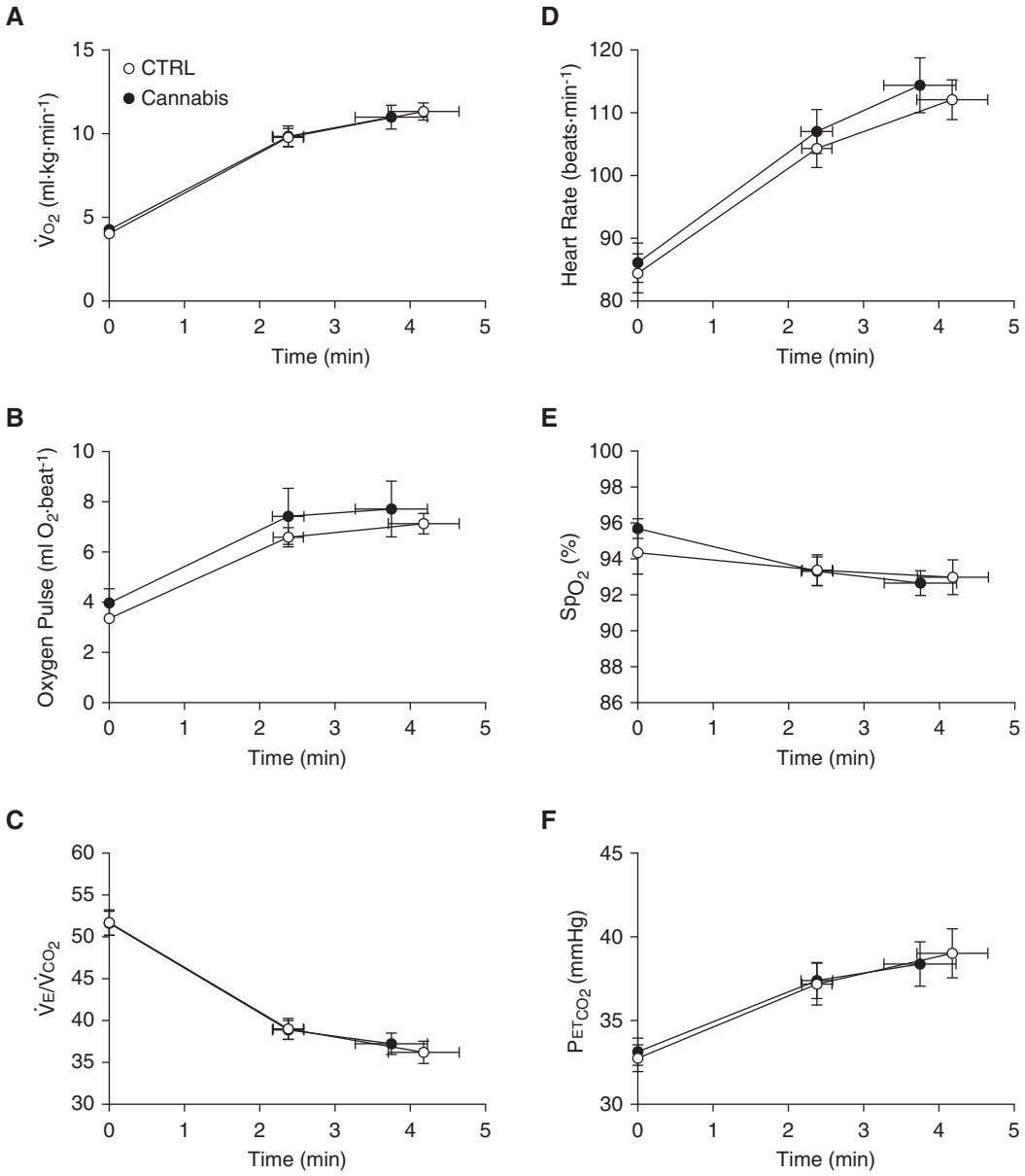

Figure 4. Effect of inhaled vaporized cannabis versus control (CTRL) on (*A*) oxygen consumption, (*B*) oxygen pulse, (*C*) the ventilatory equivalent for carbon dioxide, (*D*) heart rate, (*E*) oxygen saturation, and (*F*) the partial pressure of end-tidal carbon dioxide during symptom-limited constant-load cycle exercise testing at 75% of peak incremental power output in adults with advanced chronic obstructive pulmonary disease. Data are presented as means ± SEM. $P_{ET_{CO_2}}$ = end-tidal (partial) carbon dioxide pressure; Sp_{O_2} = oxygen saturation by pulse oximetry; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalent for carbon dioxide; $\dot{V}_{O_2}$ = oxygen consumption.

Importantly, five of the nonresponders coughed after inhalation of vaporized cannabis and reported clinically significant worsening of their exertional breathlessness at isotime after inhalation of cannabis versus CTRL (Figure 2G). Tashkin and colleagues (15) similarly reported that inhalation of 5 and 10 mg of aerosolized THC provoked a cough in four of five patients with asthma, two of whom exhibited THC-induced bronchospasm. Therefore, the cough induced by vaporized cannabis in five of the 12 nonresponders could have masked a potentially positive effect of inhaled vaporized cannabis versus CTRL on airway function, exertional breathlessness, and EET in our participants. The mechanisms mediating the THC-induced cough reflex are not fully understood. Previous studies have demonstrated that CB_1 receptor agonists may inhibit or induce bronchospasm; this dual effect of CB_1 receptor activation on bronchial responsiveness is dependent on cholinergic tone (45). As all of our participants were receiving at least

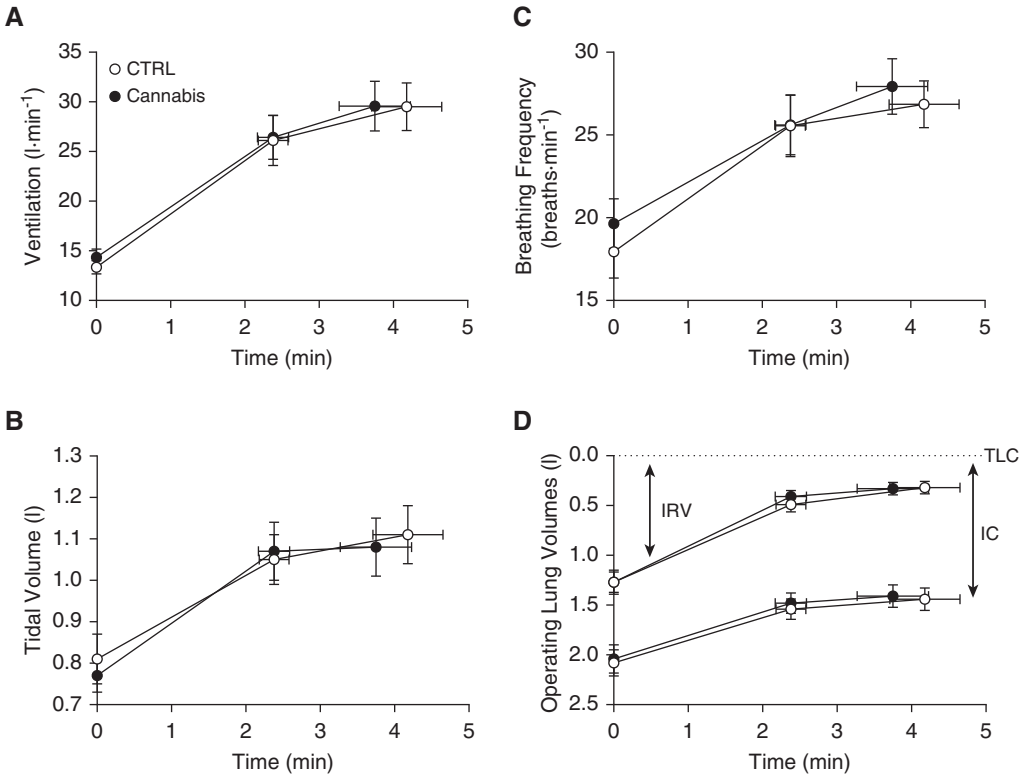

Figure 5. Effect of inhaled vaporized cannabis versus control (CTRL) on (*A*) minute ventilation, (*B*) tidal volume, (*C*) breathing frequency, and (*D*) dynamic operating lung volume responses during symptom-limited constant-load cycle exercise testing at 75% of peak incremental power output in adults with advanced chronic obstructive pulmonary disease. Data are presented as means ± SEM. IC = inspiratory capacity; IRV = inspiratory reserve volume; TLC = total lung capacity.

dual-inhalation therapy for management of their COPD, we cannot rule out the possibility that differences in bronchial smooth muscle tone may have contributed to the observed heterogeneity in the cough reflex elicited by inhalation of vaporized cannabis. Future studies should evaluate the effect of inhaled vaporized cannabis on airway function, exertional breathlessness, and EET in adults with COPD receiving anticholinergic bronchodilator therapy versus those who are not.

Neuroimaging studies evaluating the effect of cannabis on pain have demonstrated altered activity in brain regions (46) associated with negative affect and implicated in the perception of breathlessness (47), particularly its affective (unpleasantness) dimension. To this end, cannabis could alter the central perception of breathlessness and improve EET by reducing negative affect and/or increasing feelings of euphoria. Indeed, earlier studies demonstrating cannabis-induced bronchodilation often reported concomitant psychoactive effects, particularly a feeling of being "high" within minutes of treatment administration (15–18). Importantly, these studies reported a greater degree of intoxication after administration of smoked cannabis (i.e., the degree of "high" was rated ∼6 on a 7-point scale) relative to that observed in our participants after inhalation of vaporized cannabis (i.e., the degree of "high" was rated ∼4.8 on a 100-mm visual analog scale) (17). The low peak plasma THC levels achieved in our study likely account for the relatively modest effects of inhaled vaporized cannabis on psychoactivity. Nevertheless, we observed a modest but significant within-treatment effect (i.e., pre- to post-treatment) of inhaled vaporized cannabis on psychoactivity, including decreased ratings of anxiety and increased ratings of feeling high, drunk, and stoned. It is possible that the potentially positive effects of this altered psychoactive state on exertional breathlessness and EET may have been confounded by the cough reflex and its effect on exertional breathlessness exhibited in some of our participants after inhalation of vaporized cannabis. Moreover, a preliminary study of five adults with mild-to-moderate COPD by Pickering and colleagues (48) reported that sublingual administration of Sativex—a cannabis-based medicinal extract containing both THC and CBD—reduced the selection frequency of respiratory descriptors associated with air hunger, an inherently unpleasant form of breathlessness (49). By contrast, we observed no effect of inhaled vaporized cannabis versus CTRL on unpleasantness ratings of exertional breathlessness and the selection frequency of breathlessness descriptors at end-exercise.

Table 5. Pharmacokinetics of inhaled vaporized cannabis versus control in adults with advanced chronic obstructive pulmonary disease*

Metabolite	Control					Cannabis				
	Pretreatment	2 min	30 min	75 min	180 min	Pretreatment	2 min	30 min	75 min	180 min
THC, ng · ml^{-1}	—	0.82 ± 0.55	0.05 ± 0.10	—	—	—	13.91 ± 6.16†	2.18 ± 0.96‡	0.79 ± 0.44	0.14 ± 0.16
THCA, ng · ml^{-1}	—	—	—	—	—	—	0.70 ± 0.27	0.30 ± 0.15	0.09 ± 0.12	—
11-OH-THC, ng · ml^{-1}	—	—	—	—	—	—	0.87 ± 0.71	0.56 ± 0.41	0.29 ± 0.22	0.06 ± 0.10
THC-COOH, ng · ml^{-1}	—	0.08 ± 0.22	0.21 ± 0.28	0.14 ± 0.23	0.10 ± 0.21	—	1.54 ± 1.38†	3.05 ± 1.95†	2.23 ± 1.57†	1.37 ± 1.04†
CBD, ng · ml^{-1}	—	1.36 ± 0.84	0.19 ± 0.19	0.04 ± 0.10	—	—	—	—	—	—

Definition of abbreviations: 11-OH-THC = 11-hydroxy-Δ^9-tetrahydrocannabinol; CBD = cannabidiol; THC = Δ^9-tetrahydrocannabinol; THCA = *trans*-Δ^9-tetrahydrocannabinol-9-acid A; THC-COOH = 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol.

*Values represent means ± SD.

†$P < 0.0001$ in control versus cannabis.

‡$P < 0.01$ in control versus cannabis.

Earlier studies demonstrating cannabis-induced bronchodilation in healthy adults and adults with asthma often reported a concomitant increase in heart rate that was sustained for approximately 60 minutes after inhalation (15–17). In contrast to these findings, we did not observe a significant effect of inhaled vaporized cannabis versus CTRL on heart rate, presumably due to the relatively low plasma levels of THC.

Methodological Considerations

The generalizability of our results is restricted to a small and relatively homogeneous group of clinically stable and symptomatic adults with advanced COPD. Larger randomized clinical trials with more participants are needed to draw definitive conclusions regarding the effect of inhaled vaporized cannabis on exertional breathlessness, EET, and cardiopulmonary physiological parameters in adults with COPD.

We caution against the extrapolation of our results to other doses, modes (e.g., smoked, oral), types (e.g., various THC:CBD ratios), and regimens (e.g., repeat-dose) of cannabis dispensation in this patient population.

In our study, inhaled vaporized cannabis had a modest but significant within-treatment effect on some measures of psychoactivity. Future studies should utilize existing cannabinoid preparations (e.g., CBD) that do not affect psychoactivity but act on cannabinoid receptors to assess changes in airway function, exertional breathlessness, and EET in COPD.

The dried herbal cannabis material used in the CTRL arm of our trial may not have represented a "true" placebo as it contained trace amounts of CBD (<1%) that were detected in the plasma 2 minutes after vaporization. Furthermore, 12 of the 16 participants correctly identified the visit at which they received cannabis, with four of these 12 participants citing a noticeable difference in taste/smell of the inhaled vapor between cannabis and CTRL visits. Thus, a placebo devoid of THC and CBD and with the same taste and smell as the active cannabis should be identified for use in future trials

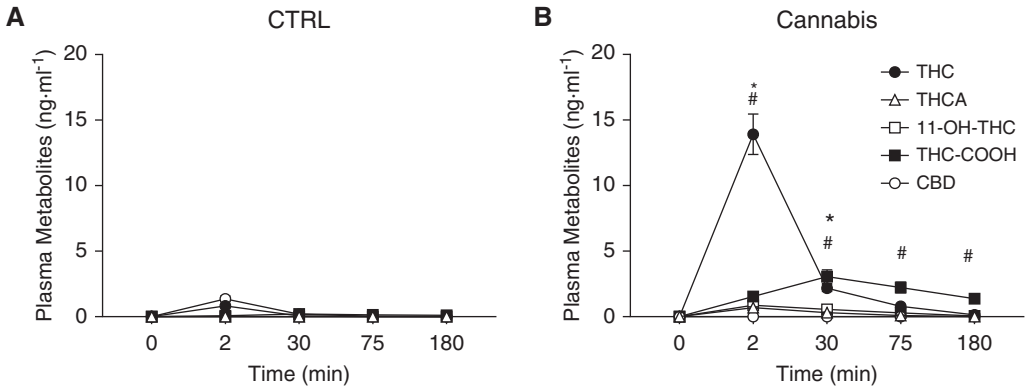

Figure 6. Effect of inhaled vaporized (*A*) control (CTRL) and (*B*) cannabis on blood biochemistry in adults with advanced chronic obstructive pulmonary disease. Data are presented as means ± SEM. 11-OH-THC = 11-hydroxy-Δ^9-tetrahydrocannabinol; CBD = cannabidiol; THC = Δ^9-tetrahydrocannabinol; THCA = *trans*-Δ^9-tetrahydrocannabinol-9-acid A; THC-COOH = 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol. *Significant difference in CTRL versus THC for plasma THC and #significant difference in CTRL versus THC for plasma THC-COOH ($P < 0.05$).

Conclusions

In 2015, the American Thoracic Society Marijuana Workgroup highlighted a need for controlled studies to evaluate the clinical effects of inhaled vaporized cannabis on lung disease, sleep, and critical illness (9). In response to this call for research, our randomized controlled trial is the first to demonstrate that 35 mg of inhaled vaporized cannabis containing 18.2% THC had no clinically meaningful positive or negative effect on exertional breathlessness, exercise endurance, and airway function in symptomatic adults with advanced COPD receiving dual- or triple-inhalation therapy for management of their underlying pulmonary pathophysiology. ■

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

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Table 6. Effect of inhaled vaporized cannabis versus control on cognitive function, mood, and psychoactivity in adults with advanced chronic obstructive pulmonary disease*

	Control		Cannabis	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Mini-Mental State Examination, out of 30	29.6 ± 0.5	29.7 ± 0.6	29.4 ± 0.9	29.6 ± 0.8
Mood Effects, 100-mm VAS				
Sad/Happy	89.5 ± 13.5	87.9 ± 12.4	89.1 ± 13.9	89.9 ± 13.3
Anxious/Relaxed	83.7 ± 22.6	89.4 ± 10.8	80.5 ± 23.3	84.7 ± 25.3
Jittery/Calm	85.2 ± 17.8	91.5 ± 8.1	81.4 ± 22.9	86.9 ± 21.1
Bad/Good	91.2 ± 10.4	89.9 ± 10.6	90.1 ± 10.2	89.9 ± 12.5
Paranoid/Self-assured	94.0 ± 6.5	92.8 ± 8.0	90.4 ± 12.8	91.6 ± 11.4
Fearful/Unafraid	90.9 ± 15.3	93.1 ± 8.1	91.9 ± 11.4	94.1 ± 6.4
Psychoactive Effects, 100-mm VAS				
Down	13.2 ± 19.1	11.6 ± 19.3	15.0 ± 19.8	12.4 ± 2.5
Anxious	9.8 ± 12.4	9.1 ± 13.8	17.6 ± 18.0	8.2 ± 1.2†
Hungry	13.2 ± 16.9	16.2 ± 18.9	12.6 ± 16.2	11.4 ± 1.5
Sedated	8.6 ± 17.0	8.5 ± 14.3	8.6 ± 18.1	8.4 ± 8.7
Impaired	5.2 ± 7.9	4.4 ± 4.6	5.5 ± 7.9	8.4 ± 1.2
Drunk	2.5 ± 2.8	3.2 ± 3.7	1.6 ± 1.6	4.5 ± 4.3†
Stoned	2.7 ± 3.1	3.7 ± 3.6	1.6 ± 1.5	6.3 ± 5.6†
High	2.8 ± 3.4	3.8 ± 3.9	1.9 ± 2.1	4.8 ± 4.5†
Good drug effects	2.4 ± 3.2	5.3 ± 7.0	1.8 ± 2.1	17.6 ± 27.8†
Bad drug effects	2.1 ± 3.0	3.2 ± 3.3	1.5 ± 1.8	4.0 ± 4.6†
Do you like the drug effects	2.1 ± 3.1	6.9 ± 12.0	2.1 ± 2.8	15.3 ± 27.7†

Definition of abbreviation: VAS = visual analog scale.
*Values represent mean ± SD.
†$P < 0.05$ versus pretreatment within condition.

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