



Early View

Research letter

Short-term effects of menthol on walking dyspnea in patients with COPD: a randomised, single blinded, cross-over study

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Short-term effects of menthol on walking dyspnea in patients with COPD: a randomised, single blinded, cross-over study

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Conflict of interest: None of the authors have any conflict of interest regarding this study.

Data sharing: All of the anonymized individual participant data collected during the trial are available (no end date). Requests should be directed to gprieur.kine@gmail.com.

Take home message: Chewing menthol gum prior to exercise is a safe, easy-to-implement, low-cost, non-pharmacologic intervention that provides a reduction in dyspnea in one third of patients and decrease the perception of discomfort during exercise in two-thirds of patients

To the editor:

Exertional respiratory discomfort is the most common symptom in patients with Chronic Obstructive Pulmonary Disease (COPD) [1]. Menthol has recently been proposed as an ergogenic aid to decrease the perception of dyspnea during exercise [2–4]. Menthol activates the Transient Receptor Potential Melastatin 8 (TRMP8) channels in the sensory nerve fibers of the tongue, promoting a feeling of freshness and a cognitive illusion of airflow into the airways [2, 5, 6]. We hypothesized that chewing menthol-flavored gum before exercise would decrease the perception of dyspnea during walking in COPD patients.

METHODS

We conducted a randomized, cross-over, multi-center trial (Groupe Hospitalier du Havre, center hospitalier de Morlaix, center Resp'Air Talence) (NCT03626519). Inclusion criteria: diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease guidelines), participation in a pulmonary rehabilitation program, functional dyspnea (modified medical research council scale ≥ 2) and consent to participation. Exclusion criteria: clinical instability (pH < 7.35 or body temperature $> 38^{\circ}\text{C}$), neurological / orthopedic disorder, difficulty with chewing and swallowing disorders.

Intervention

Participants performed the 6-minute walk test (6MWT) once during the baseline assessment for familiarization. On the test day (between 2 and 5 days after the baseline assessment), they performed two 6MWT, separated by 30 minutes of rest, in two different, randomized conditions. In the experimental condition, participants chewed menthol-flavored gum (Airwaves Extreme Menthol Extreme[®], Wrigley, Chicago, IL) for 5 minutes before the test and in the controlled condition, they chewed strawberry-flavor gum (Hollywood Strawberry Style[®], Mondelēz International, United Kingdom). No encouragement was given during the 6MWT to avoid influencing participants.

Outcome measures

The primary outcome was end-of-task dyspnea measured using the modified 0-10 Borg scale (0=no dyspnea, 10=maximal dyspnea).

Secondary outcomes were end-of-task leg discomfort (0-10 Borg scale), peripheral oxygen saturation, heart rate, tidal volume, minute ventilation, inspiratory capacity and respiratory rate (measured using Spirodoc[®] (Medical International Research, Italy)), 6 minute walking distance. After completion of both tests, participants were asked which condition they had preferred and if they felt that the menthol had had any effect.

Randomization, blinding and statistical analysis

A randomization sequence was determined for each center by the research unit using Edgar2 (<http://www.Edgarweb.Org.Uk/>) computer software (ratio 1:1). The randomized condition sequence was provided in a closed, opaque envelope with the patient's inclusion number on the front and opened by a research assistant just before the first condition. Participants could not be blinded, however their knowledge of the purpose of the study was limited to 'the impact of menthol on effort'. Assessors were blinded to the condition. This was ensured by 1) the participant chewing the gum in a closed room while the assessor waited at the test site and 2) the assessor remaining at a minimum distance of 2 meters from the participant to avoid smelling their breath. Sixty-three participants were required to detect a between conditions difference of 1 point on the modified Borg scale 0-10 (minimal clinically important difference)[7] and a moderate effect size (0.5) on end-of-task dyspnea with a power of 80% and an alpha risk \leq 0.05.

Mean differences were calculated using a mixed model adjusted for baseline values, and the sequence (order of conditions) was used to assess the carry-over effect, with participants as random effects. R-software was used (<https://www.R-project.org/>) with the packages lme4 and lmerTest [8–10]). Statistical analysis was performed blind.

RESULTS

Sixty-three patients were included between October 2019 and February 2021 (Ratio male to female : 38/25, mean age: 68 ± 20 years and mean Body Mass Index: 27 ± 7 kg/m²). Patients had severe bronchial obstruction (mean Forced Expiratory Volume in 1 second: $44 \pm 15\%$ predicted; mean Forced Vital Capacity: $76 \pm 18\%$ predicted) and lung hyperinflation (mean Residual Volume: $166 \pm 50\%$ predicted; mean Total Lung Capacity: $110 \pm 19\%$ predicted; mean Inspiratory Capacity: $77 \pm 23\%$ predicted). All participants had functional dyspnea (mean

mMRC 2.4 ± 0.6) and the COPD significantly impacted on their performance of activities of daily living (St-George's hospital questionnaire - activities limitations: mean $68 \pm 20\%$, scores range from 0 to 100. Higher scores indicate more severe limitations).

A trend towards reduced dyspnea with menthol was observed, but the benefits were trivial (table 1). The lower bound of the confidence interval did not reach the minimal clinically important difference of 1 point on the modified-Borg scale [11]. However, analysis of individual data showed that the menthol reduced dyspnea by at least 1 point in 21 participants (33%). Forty participants (63%) reported a positive effect of the menthol on their exercise tolerance. Only two participants reported having worse dyspnea in the menthol condition. No between condition differences were observed for the secondary outcomes (table1). For leg discomfort, there was evidence of a period or cross-over effect ($p=0.050$), this result should therefore be interpreted with caution. There was no evidence of a period or carry-over effect for any of the other outcomes. No baseline characteristic identified responder patients, however the confidence interval showed a trend that patients with FEV1 < 35% predicted were more likely to respond (relative risk 1.67 (CI95% 0.87 to 3.21) $p=0.16$).

DISCUSSION

Cooling sensations have previously been shown to reduce dyspnea. For example, breathing fresh air (7°C) modestly decreased dyspnea and increased peak exercise performance in patients with COPD [12]. Menthol can provide a cooling sensation by stimulating the membrane bound ion channel, TRPM-8, inducing a perceived reduction in temperature within the range of $8\text{--}28^{\circ}\text{C}$ [4]. This cooling sensation could increase the cognitive inspiratory flow and may alter the emotional and affective perception of dyspnea [2].

The results of the present study showed a clinically trivial effect of menthol on end-test dyspnea compared with the control condition, however the reduction in dyspnea reached the minimal clinically important difference in one-third of the participants and two-thirds reported a positive effect on their exercise tolerance.

We propose two explanations for this small effect. Firstly, the Borg scale may not be sufficiently sensitive to detect a between-condition difference. The study by Kanazaki et al. found a reduction in physical and mental breathing effort, air hunger, breathing discomfort, anxiety, and fear during inspiratory resistive loaded breathing in patients with COPD following olfactive stimulation by L-menthol using the Multidimensional Dyspnea Profile scale [2]. This reflects the self-reported perception of the patients in our study. Secondly, individuals often modify their level of exertion during self-paced exercise tests, based on their level of dyspnea.

This could also explain why other studies failed to show a benefit of non-pharmacological strategies on exertional dyspnea using the 6MWT [13, 14]. High-intensity constant work rate endurance tests are more sensitive for the detection of the effectiveness of an intervention [3, 15, 16].

Although no carry-over effect of menthol was observed on dyspnea, we do not know the duration of the effect of menthol and its potential impact on the next condition is not known. Future studies could perhaps include a washout period longer than 30 minutes between the two conditions.

Another explanation for the negative result is that the sensation of breathing comfort faded over the course of the test as the menthol effect dissipated: several participants reported that they mainly felt the benefit during first few minutes of the test. Studies in athletes reported a stronger effect of repeated menthol use on dyspnea and on performance [4]. The lack of an effect on ventilatory pattern is in line with the results of Kanazaki et al [2].

This study addressed a new area of research, looking at alternative and pragmatic approaches to the management of breathlessness. Future studies should take the methodological limitations that we outlined into consideration to optimize future studies in this field.

This multicenter study has several strengths: assessors were blinded to limit measurement bias and the instructions given to patients were standardized to limit a center effect. Patients were unaware that the primary outcome was dyspnea to minimize the influence on this outcome. We asked patients to be as honest as possible about how they felt about menthol, and to report both positive and negative aspects.

Chewing menthol gum prior to exercise is a safe, easy-to-implement, low-cost, non-pharmacologic intervention that provides a clinically important reduction in dyspnea in one third of patients and decreases the perception of discomfort during exercise in two-thirds of patients. Continuous release or repeated administration of menthol may have a greater effect on dyspnea reduction throughout exercise [4].

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Table 1. Effects of menthol gum versus control gum on dyspnea and physiological variables at the end of exercise

Variables	Menthol		Control		Condition effect	
	Baseline Mean (SD)	End-exercise Mean (SD)	Baseline Mean (SD)	End-exercise Mean (SD)	Adjusted mean difference (95%CI) (Menthol – Control)	p-value
Dyspnea (mBorg)	0.9 (1)	4.4 (1.6)***	1 (1.0)	4.7 (1.7)***	-0.3 (-0.5 to -0.0)	0.058
Leg discomfort (mBorg)	0.6 (1.1)	2.8 (2.1)***	0.6 (1)	2.9 (2.3)***	-0.0 (-0.3 to 0.2)	0.807
SpO ₂ (%)	92.6 (3.7)	85.7 (7)***	92.6 (3.3)	86.3 (6.2)***	-0.4 (-1.0 to 0.3)	0.255
Lowest SpO ₂	-	82.7 (7.3)	-	83.1 (6.6)	-0.4 (-1.2 to 0.3)	0.263
Heart Rate (bpm)	91.4 (17.8)	115.3 (15.2)***	92.3 (17.5)	114.5.9 (15.7)***	4.4 (-1.2 to 9.9)	0.124
Respiratory Rate (cpm)	18.6 (4.6)	24.1 (9.5)***	19 (5.2)	24.1 (5.9) ***	0.3 (-2.1 to 2.6)	0.827
Tidal volume (liters)	0.8 (0.3)	1.1 (0.5) ***	0.8 (0.4)	1.1 (0.5)***	0.0 (-0.0 to 0.1)	0.172
Minute ventilation (L/min)	13.9 (5 .1)	25.6 (9.3)***	14.7 (5.6)	25.8 (9)***	-0.1 (-1.5 to 1.3)	0.924
Inspiratory capacity (liters)	1.8 (0.6)	1.7 (0.6)**	1.9 (0.7)	1.8 (0.7)	-0.0 (-0.2 to 0.1)	0.449
6MWD (meters)	-	461.1 (124.2)	-	458.7 (124.9)	2.6 (-4.1 to 9.4)	0.447
6MWD (% pred)	-	73.1 (20.7)	-	72.8 (20.7)	0.37 (-0.76 to 1.5)	0.495

Continuous data are presented as means (SD) and as means and 95% confidence intervals for the difference between the two conditions. Mean differences were calculated using a mixed model adjusted for baseline values, and the sequence (order of conditions) was used to assess the carry-over effect, with participants as random effects. Within-condition changes (before-after test) were compared using a paired t-test. * $p < 0.05$. ** $p < 0.01$ for before-after analysis of a condition. *** $p < 0.001$ for before-after analysis of a condition. mBorg, modified Borg scale from 0 to 10 (0: no fatigue or dyspnea, 10: maximal fatigue or dyspnea). For leg discomfort, there was evidence for a period or cross-over effect ($p = 0.050$), this result should be taken with caution. There was no evidence of a period or cross-over effect on the other outcomes. Abbreviation list: bpm: beat per minute; cpm: cycles per minute; SpO₂: oxygen pulsed saturation; L: liters; 6MWD: 6 minute walking distance.