

THE EFFECT OF MINDFULNESS MEDITATION ON COUGH REFLEX SENSITIVITY

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ABSTRACT

Background-Chronic cough is common and medical treatment can be ineffective. Mindfulness is a psychological intervention that aims to teach moment-to-moment non-judgemental awareness of thoughts, feelings and sensations.

Method-30 healthy subjects and 30 chronic cough patients were studied in two sequential trials. For both studies, cough reflex sensitivity to citric acid (C5) was measured on two occasions with urge-to-cough rated following each inhalation; between challenges subjects were randomised to (i) no intervention (ii) mindfulness or (iii) no intervention but modified cough challenge (subjects suppress coughing). For the healthy volunteers, measures were one hour apart and mindfulness was practiced for 15 minutes. For the chronic cough patients measures were 1 week apart and mindfulness practiced daily for 30 minutes.

Results-In healthy volunteers, median change (IQR) in cough reflex sensitivity (logC5) for no intervention, mindfulness and suppression was +1.0(0.0 to +1.3), +2.0(+1.0 to +3.0) and +3.0(+2.8 to +3.0) doubling concentrations (dc) ($p=0.003$); significant reductions for both mindfulness ($p=0.043$) and suppression ($p=0.002$) over no intervention. In cough patients, median change (IQR) in logC5 for no intervention, mindfulness training and voluntary suppression was 0.0(-1.0 to +1.0), +1.0(-0.3 to +1.0) and +1.0(+1.0 to +2.0)dc, ($p=0.046$); significant reduction for suppression ($p=0.02$) but not mindfulness ($p=0.35$). Urge-to-cough did not change after mindfulness compared to control in either healthy ($p=0.33$) or chronic cough subjects ($p=0.47$).

Conclusion-Compared to control, mindfulness decreased cough reflex sensitivity in healthy volunteers, but did not alter cough threshold in chronic cough patients. Both groups were able to suppress cough responses to citric acid inhalation.

INTRODUCTION

Chronic cough, defined as cough lasting > 8 weeks, has a prevalence of around 12 % in the general population[1] and is associated with significant co-morbidity including anxiety and depression[2]. Despite comprehensive investigation, it is increasingly recognised that a proportion of patients fail to respond to treatment targeted at identified potential causes [3, 4]. For these patients both effective anti-tussive treatments and supportive interventions are lacking despite the acknowledgement that chronic cough is associated with significant physical, psychological and social burdens. The effect of psychological interventions on cough reflex sensitivity and whether such interventions are useful in the management of patients with chronic cough have not been investigated.

An out-patient Mindfulness Based-Stress Reduction (MB-SR) program, developed by Kabat-Zinn[5], teaches moment-to-moment non-judgemental awareness of thoughts, feelings and sensations[6] and has proven effective in the management of several chronic disease states including chronic pain[7], depression[8], fibromyalgia[9] and psoriasis[6]. Mindfulness training is classically led by experts and practiced in group sessions over an 8-10 week period with regular homework activities to encourage integration of the coping strategies into everyday life. A 10 week MB-SR group-based program directed at fibromyalgia patients reduced subjective ratings of physical and psychosocial symptoms[9]. Prolonged psychological benefits were demonstrated in a 4-year study of 225 patients with chronic pain who had participated in an intensive 8 week MB-SR program although the initial reductions in the Pain Rating Index (PRI) returned to pre-intervention levels at 6 months[7]. However there is some evidence to suggest that mindfulness training can be effective at reducing disease severity. In moderate to severe psoriasis, customised mindfulness tape recordings, played during individual phototherapy treatment, accelerated rates of skin clearing compared to a “no-tape” control group[6].

Cough can be experimentally induced by chemical stimulation of pulmonary afferent nerve fibres. The concentration of inhaled citric acid or capsaicin eliciting five or more coughs in the first minute after inhalation, known as the C5, is a reproducible measure of cough reflex sensitivity[10] and is known to be moderately correlated with objective cough frequency in respiratory conditions[11]. Cough reflex sensitivity can not be used to reliably differentiate between health and disease since there is considerable overlap of C5 in healthy subjects and patients with chronic cough, but on average chronic cough subjects have a lower C5 (more sensitive reflex)[10], which increases following successful treatment of the cough[12].

Anecdotally patients with chronic cough often describe a sensation of irritation located in the throat which provokes spontaneous coughing. An ‘urge-to-cough’ also occurs during the inhalation of capsaicin and citric acid, increasing in magnitude dose-dependently and preceding the motor cough response[13]. However, the cough reflex is under considerable voluntary control. Healthy volunteers are able to resist the urge-to-cough and voluntarily suppress coughing during capsaicin challenge[14].

The urge-to-cough is an unpleasant sensation that may be associated with negative cognitions, especially in circumstances where coughing would be maladaptive. Psychological interventions aimed at reducing the negative cognitions associated with the experiencing the urge-to-cough may reduce magnitude of the urge-to-cough sensation and therefore reduce cough reflex sensitivity. We hypothesised that a mindfulness intervention would reduce perceived urge-to-cough on inhaling tussive agents and therefore reduce motor cough response and cough reflex sensitivity. Two randomised controlled trials were performed assessing the effect of mindfulness on cough reflex sensitivity; firstly testing the

immediate effect of mindfulness in healthy volunteers and secondly a short duration out-patient intervention program in patients with chronic cough.

METHODS

Subjects

Thirty healthy volunteers and thirty patients presenting with chronic cough (> 8 weeks duration) to a tertiary referral cough clinic (University Hospital of South Manchester) were studied. Subjects performed a baseline citric acid cough challenge and were excluded from further participation if they did not have a measurable C5 i.e. did not cough 5 times after inhaling the maximum concentration of citric acid. Other exclusion criteria were a history of recent upper respiratory tract infection (<4 weeks) or current treatment with opiates, ACE-inhibitors or any over-the-counter cough medicines. Current smokers were also excluded. The chronic cough patients had received targeted 8 week treatment trials for underlying gastro-oesophageal reflux disease, asthma and/or upper airway cough syndrome (UACS). None of the patients had undergone any behavioural therapy for their cough. Ethical approval was granted by the local research ethics committee and written informed consent obtained from all subjects

Study Design

Two sequential studies were performed. Firstly, the immediate effects of a mindfulness intervention on cough reflex sensitivity were tested in healthy volunteers to assess the ability of a relaxation technique to modulate the cough reflex. Secondly, we examined the effect of mindfulness on cough reflex sensitivity in chronic cough subjects. This study was of similar design but mindfulness was taught and practiced over a period of one week to investigate the longer term effects of mindfulness in a patient group and therefore its potential as a treatment.

Study 1: Immediate Effect of Mindfulness in Healthy volunteers

Cough reflex sensitivity was measured at baseline using a citric acid challenge, following which subjects were randomised to one of three possible groups; (i) no intervention (control), (ii) mindfulness training or (iii) voluntary suppression. Randomisation by minimisation was performed and subjects were stratified according to cough reflex sensitivity and gender [15].

Control: Repeat citric acid challenge was according to the standard protocol described below after 1 hour..

Mindfulness Intervention: A 15 minute mindfulness training exercise was performed just prior to their second cough challenge at 1 hour.

Voluntary Suppression: No intervention was performed between baseline and repeat citric acid challenges at 1 hour but at the beginning of the repeat challenge subjects were instructed to try not to cough and reminded of this following each subsequent inhalation of citric acid. Patients were not provided with any particular strategies to achieve this.

Study 2: Effect of Mindfulness Course in Chronic Cough

As for study 1, chronic cough patients had cough reflex sensitivity testing at baseline but also the Spielberger State-Trait Anxiety Inventory (STAI) and then were randomised/stratified in the same manner to (i) no intervention, (ii) mindfulness training or (iii) voluntary suppression. However repeat cough challenges for this study were performed after a longer interval, 7-10 days later, to allow a more prolonged mindfulness intervention. For this mindfulness intervention cough patients took part in an educational interview delivered by the researcher during which meditative techniques were explained. The interview was recorded on an audio-cassette for home practice, at least 30 minutes per day until their return visit. Patients did not keep a record of their compliance with home practice.

Procedures

Citric Acid Challenge

Citric acid cough challenge was performed using the single-breath, doubling dose method, delivered by a dosimeter (Koko dosimeter, Ferraris Ltd) with inspiratory flow rate limitation[16]. In brief, serial doubling concentrations of citric acid ranging from 0.03 M to 4 M were administered 1 minute apart with 3 interspersed placebo inhalations (normal saline) to which both researcher and subject were blinded. Subjects were instructed to cough freely and not try to suppress coughing (except in voluntary suppression challenges). The number of coughs, defined as explosive sounds, that occurred in the minute after each inhalation was recorded and the test stopped when the subject coughed at least 5 times (C5). To ensure consistency the same nebuliser pot was used throughout the experiment for each individual, and re-calibrated at regular intervals. Spirometry was performed before and after each challenge and if FEV₁ fell by $\geq 20\%$ following citric acid inhalation subjects were excluded from further study.

Urge-to-Cough

Following each inhalation of citric acid healthy subjects were asked to rate their urge-to-cough intensity on a visual-analogue scale (VAS) from 0-100 mm anchored by “no urge” to “severe urge”. Chronic cough patients rated their urge-to-cough on a modified Borg scale ranging from 0 (no need to cough) to 10 (maximum urge-to-cough) as described by Davenport[13].

Mindfulness intervention

The mindfulness intervention aimed to train subjects to experience sensations without evaluation or judgment. We predicted that mindfulness would enable subjects to experience the urge to cough without focussing on either the possibility of coughing or on any associated distress. The intervention was adapted for this study by psychologists and intended to be delivered by non-experts after brief training. For this study a breathing exercise was used to aid mindfulness[5]. Subjects were given written instructions consisting of an explanation of the principles of mindfulness and then specific directions as to how to perform the breathing and mindfulness exercises (see online supplement). Subjects are asked to notice their breathing and the sensations associated with it but not consciously try to change their breath or relax. They were seated in a quiet room, and told to close their eyes and focus on their breathing ‘being with each inhalation’ for its full duration and ‘with each exhalation’ for its full duration. Subjects were instructed to return their attention to their breathing each time they noticed their mind had wandered. This exercise was conducted with support from the researcher. Healthy volunteers spent 15 minutes practising the mindfulness exercise prior to the cough challenge. Chronic cough subjects were given the same instructions and asked to practice the exercise at home for at least 30 minutes per day until the next visit.

State/Trait Anxiety

The Spielberger State-Trait Anxiety Inventory (STAI) is a self-report scale for measuring state (present) and trait (general) anxiety levels that has been used extensively in research[17]. State anxiety is sensitive to change following intervention. Cough patients completed the scale at baseline and at repeat cough challenge.

Statistical Analyses

Cough reflex sensitivity was log transformed (LogC5) prior to analysis. The Kruskal Wallis test was used to compare change in cough reflex sensitivity, urge to cough rating at C5 and anxiety scores across the three groups. Where the Kruskal Wallis test suggested a significant difference, post hoc pair-wise comparisons were made with the Mann Whitney test.

RESULTS

Thirty healthy volunteers (24 female, 6 male) and 30 cough patients (20 female, 10 male,) meeting eligibility criteria took part in the studies. Mean age was 34 years (SD 10.5) in healthy subjects compared to 58 years (SD 9.46) in the cough patients. None of the participants were current smokers but 11 (37 %) of the cough patients were ex-smokers >6 months, with a median smoking history of 0.0 (0 to 45) pack years. Pre-challenge mean % predicted FEV₁ was 104.98 % (SD 13.45) in healthy subjects compared to 97.04% (SD 20.45) in the cough patients. Age, gender and baseline C5 are compared between randomisation groups in table 1. Significantly more females were randomised to mindful intervention in the healthy volunteer study, but groups were otherwise well-matched.

Table 1 – Age, Gender and Baseline C5 Compared by Randomisation Group

		No Intervention	Mindfulness Training	Voluntary Suppression	P value
Healthy Volunteers	Number	10	10	10	
	Mean (SD) Age	34.4 (11.1)	33.1 (11.1)	34.4 (10.2)	0.921
	Gender M:F*	3:7	1:9	2:8	0.001
	Median (IQR) Baseline logC5	-0.2M (-0.4 to 0.0)	-0.9M (-0.9 to 0.0)	-0.2M (-0.3 to 0.0)	0.062
Chronic Cough Subjects	Number	11	10	9	
	Mean (SD) Age	54.2 (10.8)	60.2 (8.1)	61.11 (8.4)	0.350
	Gender M:F*	3:8	3:7	4:5	0.068
	Median (IQR) Baseline logC5	-0.9M (-1.5 to 0.0)	-0.8M (-1.3 to -0.5)	-0.9M (-0.9 to -0.3)	0.798

Comparisons made by Kruskal Wallis test except where marked *Chi-squared test.

Study 1: Healthy Subjects

Baseline median (IQR) logC5 for all healthy volunteers was -0.3M (-0.6 to 0.0). Ten subjects were randomised to each group and median change (IQR) in logC5 for no intervention, mindfulness intervention and voluntary suppression groups was +1.0 (0.0 to +1.3), +2.0 (+1.0 to +3.0) and +3.0 (+2.8 to +3.0) doubling concentrations respectively, p=0.003. The mindfulness intervention significantly reduced cough reflex sensitivity compared to the no intervention group (p=0.043). Voluntary suppression of coughing also significantly improved cough reflex sensitivity (p=0.002) but was not significantly better than the mindfulness intervention (p=0.052) (see figure 1).

Urge-to-cough data was available in 18 (60 %) of healthy subjects and showed a log-linear relationship with concentration of citric acid (online supplement figure E1). Median (IQR) baseline urge-to-cough at C5 (rated on a VAS from 0 to 100mm) was 92mm (69 to 99). Median change (IQR) in urge-to-cough at C5 for no intervention, mindfulness and voluntary suppression groups was +3mm (-4 to +32), +1mm (-23 to +3) and +13mm (+3 to +55.3) respectively, with a trend towards a difference between the groups (p=0.069). There was no statistically significant difference in change in urge-to-cough at C5 between no intervention

and mindfulness groups ($p=0.31$) or between no intervention and voluntary suppression groups ($p=0.39$) but the suggestion of a lower urge to cough for the mindfulness group compared to voluntary suppression ($p=0.015$), (see figure 2).

Study 2: Cough Patients

Baseline median (IQR) log C5 for all patients was -0.9M (-1.2 to -0.3); significantly lower than in the healthy volunteer study ($p=0.001$). Eleven patients were randomised to no intervention, 10 to the mindfulness program and 9 to voluntary cough suppression. Median change (IQR) in log C5 for no intervention, mindfulness and voluntary suppression groups was 0.0 (-1 to +1), +1.0 (-0.3 to +1) and +1.0 (+1.0 to +2.0) doubling concentrations respectively, ($p=0.046$). There was no statistically significant difference in change in LogC5 between no intervention and mindfulness groups ($p=0.35$). Comparison of controls and voluntary suppression groups revealed a significant difference ($p=0.02$) with an increase in cough threshold (see figure 3).

Urge-to-cough data was collected for all patients. Median (IQR) baseline urge-to-cough at C5 as rated by a Modified Borg scale was 4 (3 to 6.3). Median change (IQR) in urge-to-cough at C5 was not significantly different between no intervention, mindfulness and voluntary suppression groups [0 (-2 to +1), 0 (0 to +2), and 0 (-1 to +1) respectively, ($p=0.70$)], figure 4

Compared to a working population sample mean [17] both male and female cough patients had high trait anxiety levels (mean (SD) in males 36.60 (16.21) v 34.89 (9.19), in females 40.50 (11.00) v 34.79 (9.22)) but below average state anxiety scores (mean (SD) in males 30.50 (10.30) v 35.72 (10.40), in females 34.15 (8.83) v 35.20 (10.61)). There were no significant changes in either in state ($p=0.23$) or trait ($p=0.78$) anxiety for any of the patient groups.

DISCUSSION

In this study we have shown that healthy volunteers undergoing a mindfulness intervention had a prompt reduction in cough reflex sensitivity compared to a no intervention control group. Chronic cough patients performing a brief out-patient mindfulness program however had no change in cough reflex sensitivity compared to controls. Mindfulness did not significantly alter the perceived urge-to-cough at the C5 cough threshold in either subject group and did not appear to reduce state-trait anxiety levels in the chronic cough patients compared to control. Voluntary suppression of coughing after citric acid inhalation was able to significantly decrease cough reflex sensitivity in both trials, but appeared to be more effective in the healthy volunteers than chronic cough patients.

There are a number of possible explanations for the failure of mindfulness to alter cough reflex sensitivity in the chronic cough study compared to the healthy volunteer study. Firstly, the healthy volunteer study was designed to assess any immediate effect of mindfulness training. In contrast, the chronic cough study assessed whether more prolonged mindfulness training might have a clinical role in this distressing condition. It is possible that any improvements in cough reflex sensitivity following a mindfulness exercise are only very short-lived, however the optimal duration of mindfulness training is not known. A longer more intensive supervised course may be required to have a prolonged effect in patients than in healthy volunteers, although this has never been investigated. Secondly, cough reflex sensitivity in chronic cough patients may be more resistant to change. Voluntary suppression

reduced cough reflex sensitivity in chronic cough patients but appeared to be less effective than in healthy controls. This is in keeping with the experience of chronic cough patients who complain of an inability to control coughing leading to social embarrassment [18]. During cough challenges, as the intensity of the urge-to-cough increases, the ability to suppress coughing decreases until coughing becomes an irresistible response. We speculate that in chronic cough patients coughing may result not only from an increased sensitivity to irritants but also from poorer conscious control over coughing which may be mediated by impairment of descending cortical pathways. This could also explain why psychological interventions such as mindfulness may be less effective than in healthy volunteer studies.

It may be important that this mindfulness training encouraged subjects to focus on their breathing. Attending to the sensations associated with inhalation and exhalation rather than the urge-to-cough may have motivated the individual to prioritise continued breathing over coughing. This could explain the effect of mindfulness in the healthy volunteer group. It would be interesting to explore whether mindfulness of another non-respiratory bodily sensation or external influence (e.g. music) would have a similar inhibitory effect on behavioural cough response.

We found no statistically significant change in the urge to cough experienced for any subject group in either study, but as a secondary endpoint, the studies may well have been inadequately powered to demonstrate such effects. We hypothesised that mindfulness would reduce cough reflex sensitivity by reducing the urge to cough and that voluntary suppression would also reduce cough reflex sensitivity but at the expense of a more intense urge to cough. In the healthy volunteer study, despite some missing data, there was a suggestion that the urge to cough at C5 was lower in the mindfulness group compared to voluntary suppression.

Some studies investigating the effect of a mindfulness intervention in chronic disease have lacked control groups[6, 7, 9] thereby not excluding a significant placebo effect from such treatment. We compared this mindfulness intervention to both a no intervention control group and additionally included a modified cough challenge to act as a positive control, during which volunteers were instructed to “try not to cough”. In the healthy volunteer study, cough reflex sensitivity did improve by one doubling dose in the control group, however, it is interesting to note that in the chronic cough study there was no such improvement with no intervention (decreased C5 in 23 of 30 healthy volunteers versus 11 of 30 chronic cough patients).

The main limitation of this study is that the duration and intensity of the mindfulness program was inadequate and we cannot be certain that the chronic cough patients complied with home practice. However, our aim was to assess whether a brief intervention delivered by non-experts could be effective. Other studies with positive outcomes with symptoms other than cough have used an intensive 8-10 week program and taught formal mindful meditative techniques such as yoga, body scan and sitting meditation[7, 8]. Introduction of these formal techniques and modification of the program by psychologists to be more in line with the specific concerns of a group of chronic cough patients could improve future results. Also despite stratification, a greater proportion of females were randomised to the mindfulness intervention in the healthy volunteer study. Subjects were however reasonably well matched for baseline cough reflex sensitivity, which is likely to be more important.

In summary, the findings of this study suggest a short-duration mindfulness out-patient program cannot be recommended as a psychological intervention for chronic cough, although a potentially beneficial effect following a more prolonged intervention led by experts is not excluded. Since voluntary suppression reduced cough reflex sensitivity in both subject groups, a future randomised controlled study of voluntary cough suppression as a therapeutic

strategy for chronic cough would be interesting, particularly to investigate whether prolonged practice improves ability to successfully suppress coughing. Indeed speech and language therapy is the only supportive intervention shown to be effective in chronic cough patients[19], a component of which is strategies to suppress or replace the cough.

FIGURES LEGENDS

Figure 1: Changes in cough reflex sensitivity to citric acid in healthy volunteers for control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values and error bars interquartile range.

Figure 2: Changes in urge to cough at citric acid cough threshold (C5) in healthy volunteers for control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values and error bars interquartile range.

Figure 3: Changes in cough reflex sensitivity to citric acid in chronic cough patients for control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values and error bars interquartile range.

Figure 4: Changes in urge to cough at citric acid cough threshold (C5) in chronic cough patients for control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values and error bars interquartile range.

Figure E1: Relationships between capsaicin concentration and urge to cough. The mean urge to cough is shown (error bars standard deviation) at cough threshold (C5) and for the 5 preceding concentrations leading up to this.

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ONLINE SUPPLEMENT

Mindfulness Protocol

Many people find that most of the time their attention is focused in the past and the future more than in the present. You may yourself be aware that when you talking to one person you are already thinking about what you need to do afterwards. Similarly many people who drive have had the experience of being so wrapped up in their thoughts about what they will do when they get to their destination, they have barely even noticed the route they have driven. Mindfulness is the process of becoming more aware of where you are 'in the present'. This is often helpful for people as they are then free to deal with situations as they actually are, rather than as might become or have previously been. I am going to describe a breathing exercise which is used to aid mindfulness. Before I do this, there are a number of points to bear in mind:

1. When you are doing the breathing exercise your only task is to notice your breathing and the sensations association with it. This might include the feel of the air coming in and out, the feel of the movement of muscles and the feel of your stomach moving as you breathe.
2. Paying attention to your breathing means only that. You are not to consciously try to change your breath or make yourself relax.
3. You do not need to think about you breathing, rather that you should be aware of it and notice the sensations associated with it.
4. It is best to use diaphragmatic breathing for this exercise. To do this, put your hand on your stomach and feel as you try to push your stomach out when you breath in and in when you breath out. It can take a little time to get comfortable with this type of breathing, so practise it a few time now before the exercise begins.
5. Once you are comfortable with diaphragmatic breathing you are ready to start the mindfulness exercise. This will last 15 minutes and when the time is up I will ask you to open your eyes and refocus on your surroundings. I will give you some brief instructions and then after that I will not speak unless this is necessary for the rest of the exercise.

Mindfulness Exercise

1. Find a comfortable sitting position with your spine straight and let your shoulders drop.
2. Close your eyes.
3. Bring your attention to your stomach, feeling it rise or expand gently on the in-breath and fall or recede on the out-breath
4. Keep focusing on your breathing 'being with' each in-breath for its full duration and with each out-breath for its full duration, as if riding the waves of your own breathing.
5. Every time you notice that your mind has wandered off the breath, notice what it was that took you away and then gently bring your attention back to your stomach and the feeling of breath coming in and out.
6. If your mind wanders aware from the breath a thousand times , then your 'job' is simply to bring it back to the breath every time, no matter what it becomes preoccupied with.
7. Notice what it feels like to spend time just being with your breath without having to do anything.









