ASTHMA

Double blind randomised controlled trial of two different breathing techniques in the management of asthma

C A Slader, H K Reddel, L M Spencer, E G Belousova, C L Armour, S Z Bosnic-Anticevich, F C K Thien, C R Jenkins

doi: 10.1136/thx.2005.054767

See end of article for authors' affiliations

Correspondence to: C A Slader, Faculty of Pharmacy, University of Sydney, New South Wales, Australia 2006; cassandra@pharm.usyd.edu.au

Received 20 October 2005
Accepted
23 February 2006

Background: Previous studies have shown that breathing techniques reduce short acting β agonist use and improve quality of life (QoL) in asthma. The primary aim of this double blind study was to compare the effects of breathing exercises focusing on shallow nasal breathing with those of non-specific upper body exercises on asthma symptoms, QoL, other measures of disease control, and inhaled corticosteroid (ICS) dose. This study also assessed the effect of peak flow monitoring on outcomes in patients using breathing techniques.

Methods: After a 2 week run in period, 57 subjects were randomised to one of two breathing techniques learned from instructional videos. During the following 30 weeks subjects practised their exercises twice daily and as needed for relief of symptoms. After week 16, two successive ICS downtitration steps were attempted. The primary outcome variables were QoL score and daily symptom score at week 12.

Results: Overall there were no clinically important differences between the groups in primary or secondary outcomes at weeks 12 or 28. The QoL score remained unchanged (0.7 at baseline *v* 0.5 at week 28, $p=0.11$ both groups combined), as did lung function and airway responsiveness. However, across both groups, reliever use decreased by 86% ($p<0.0001$) and ICS dose was reduced by 50% ($p<0.0001$; $p>0.10$ between groups). Peak flow monitoring did not have a detrimental effect on asthma outcomes.

Conclusion: Breathing techniques may be useful in the management of patients with mild asthma symptoms who use a reliever frequently, but there is no evidence to favour shallow nasal breathing over non-specific upper body exercises.

Breathing techniques are among the most popular complementary medicine modalities used by people with asthma.[1–4] A Cochrane review concluded that breathing exercises for asthma, such as Buteyko, yoga and diaphragmatic breathing, led to decreased use of short acting β agonists and a trend towards improvement in quality of life, but no consistent evidence of improved disease control such as reduced requirement for anti-inflammatory medication, reduced airway hyperresponsiveness, or improved lung function.[5] Some proponents of breathing techniques have suggested that the failure to demonstrate improvement in lung function measures such as ambulatory peak expiratory flow (PEF) was due to the deep inspirations and forced expirations required with such monitoring.[6] Additionally, the Cochrane review[5] highlighted the need for further studies to evaluate the impact of breathing techniques on symptom free days, physiological measurements, and airway inflammation.

This study was designed to test the hypothesis that breathing techniques aimed at reducing tidal volume and rate of breathing and encouraging the nasal route of breathing would result in greater improvement in asthma symptoms and measures of disease control, and allow a greater reduction of inhaled corticosteroid (ICS) use than non-specific upper body exercises. A secondary hypothesis was that twice daily peak flow monitoring has no detrimental effect on asthma outcomes during treatment with either form of breathing exercise.

METHODS

Subjects

The study was conducted at a respiratory research institute in Sydney and a tertiary referral hospital in Melbourne, Australia. Subjects with stable suboptimally controlled asthma were identified from a database of volunteers and from advertising in the lay press. All subjects gave informed written consent and the institutional ethics committees of Royal Prince Alfred Hospital, Camperdown and The Alfred Hospital, Melbourne approved the study. Inclusion criteria were: age 15–80 years, as-needed reliever use ≥4 occasions/week, use of ICS (≥200 μg/day for ≥3 months with no dose change during the previous 4 weeks), current non-smoker, forced expiratory volume in 1second (FEV_1) ≥50% and <90% predicted or FEV_1/forced vital capacity (FVC) ratio <70%, reversibility ≥200 ml to bronchodilator within previous 6 months, and daily access to television/video player. Exclusion criteria included current smoking or >10 pack-year smoking history, recently unstable asthma, and prior tuition in Buteyko (for full details see online supplement at http://www.thoraxjnl.com/supplemental).

Study design

The study was a double blind, randomised, controlled, multicentre comparison of two breathing techniques—one (group A) aimed at reducing tidal volume, reducing hyperventilation and encouraging nasal route of breathing, and the other (group B) involving non-specific upper body mobility exercises. After a 2 week run in period on pre-existing treatment, subjects were randomised (fig 1) using computer generated permuted blocks (block size of four). Subjects learned and practised their exercises by video instruction (see details under Interventions section and in table 1). They were asked to practise their routine exercises

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; PEF, peak expiratory flow

twice daily (approximately 26 minutes). For symptoms normally requiring reliever, subjects in both groups were advised to use a shorter set of their allocated breathing exercises (3–5 minutes) first and to take reliever if symptoms persisted. Dose reductions in ICS of 50% were attempted at weeks 16 and 22 for eligible subjects (see online supplement).

Interventions

In the videos the duration, format, and style of presentation were matched for both groups. All subjects were provided with a detailed ''Instruction'' video for initial teaching and a ''Daily Exercises'' video. They were instructed to practise their exercises twice daily, watching the video at least once daily. The ''Instruction'' video could be used again at any time. An unblinded research assistant contacted the subjects at 2 weekly intervals to review the essential elements of the breathing exercises, answer questions, and clarify concerns. Subjects were also offered face to face tuition.

Outcome measurements

All measurements were made by trained research assistants who were blinded to the subjects' treatment allocation. Baseline data were collected at week 0. At each visit, spirometry was measured and airway resistance was recorded using the forced oscillation technique.[7] Route of breathing (primarily nasal, primarily oral, mixed) was established from headset mounted thermistor recordings, and end tidal CO_2 measurements from exhaled breath, while subjects were distracted with questionnaire tasks. Airway responsiveness to mannitol[8] was assessed at all visits except week –2. Patient and Physician Global Assessments of Asthma Control were recorded on a visual analogue scale at all visits, and the Asthma Control Questionnaire (ACQ)[9] and Asthma Quality of Life Questionnaire-Sydney (AQLQ)[10] range 0–4 (best–worst quality of life) were administered at all visits except week 6.

Subjects used electronic diary spirometers (AM2, Erich Jaeger GmbH, Hoechberg, Germany) twice daily to record symptom intensity, night waking, use of reliever, Global Assessment of Asthma Control, time spent doing routine study exercises, and number of times exercises were used for symptom relief. FEV_1 and PEF were obtained from the three 2 week periods of spirometric recordings (fig 1).

Changes in medications, exacerbations, and adverse events were recorded at all visits. Moderate exacerbations were defined as ⩾2 consecutive days of increased reliever use by >2 occasions/day and/or increase in symptoms (⩾1 episode of nocturnal asthma/night and/or early waking requiring reliever) over baseline, and/or in the investigator's opinion the subject was experiencing an exacerbation. They were treated with double dose ICS for 2 weeks. Severe exacerbations were defined by requirement for oral corticosteroids.

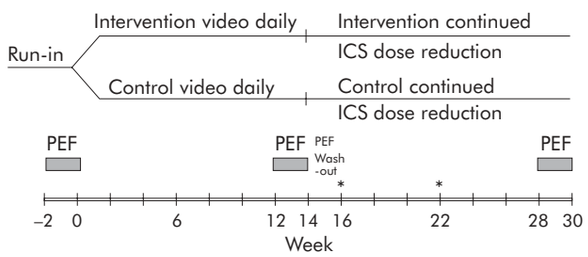

Figure 1 Schematic of study design. Inhaled corticosteroid (ICS) dose remained constant until week 16, after which two successive dose reductions of 50% were attempted for subjects who satisfied the eligibility for reduction criteria (weeks 16 and 22). *ICS dose reduction if clinically indicated (both groups).

Table 1 Exercise descriptions

	Group A	Group B*
Daily exercises		
Components	Hypoventilation	Shoulder rotations, forward curls, arm raises with controlled inspiratory-expiratory cycles
	Breath hold at functional residual capacity	''Control of breathing'': focusing on good posture and relaxation
	Nasal route of breathing	Route of breathing not specified, with both mouth and nasal breathing demonstrated
Twice daily routine	Above components performed in: 3 minute cycles for approximately 13 minutes While seated Accompanied by footage of scenery	Above components performed in: 3 minute cycles for approximately 13 minutes While seated
Symptom relief exercises		
	Shorter version of routine exercises	''Control of breathing'' exercises with or without physical manoeuvres
	Reliever use instruction: If symptoms are not relieved at first by the exercises, try them again If symptoms persist, use reliever	Reliever use instruction: If symptoms are not relieved at first by the exercises, try them again If symptoms persist, use reliever

*These exercises were designed to avoid impact on upper body muscle strength.

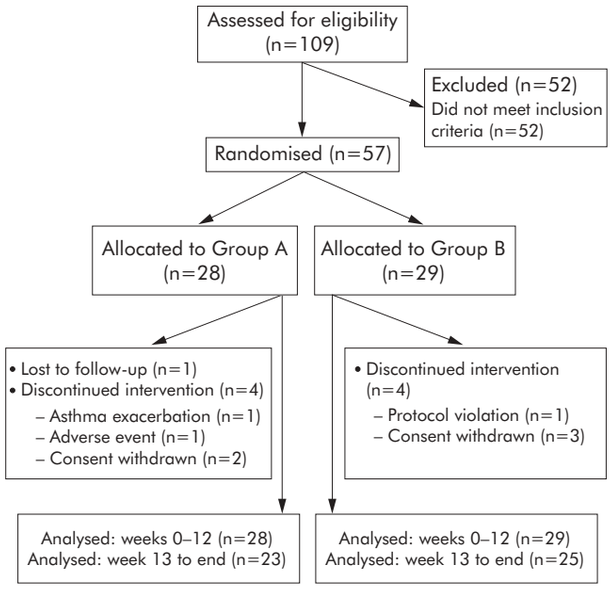

Figure 2 Patient disposition.

Analysis of data

Analysis was based on intention-to-treat, with all data from both centres combined. Handling of subject withdrawals and missing data are described in the online supplement.

The primary outcome analyses were AQLQ (total) score and daily symptom score between groups at week 12 (completion of ICS maintenance phase), with adjustment for baseline. All outcome variables were compared between groups at weeks 12 and 28. Outcome variables were also compared within groups at weeks 12 and 28. The impact of PEF monitoring was assessed by comparing outcome vari-

Table 2 Baseline demographic and clinical characteristics of the study population

Characteristic	Group A (n = 28)	Group B (n = 29)	p value
Sex (M : F)	11 : 17	14 : 15	0.6768
Smoking history (never : former)	19 : 9	23 : 6	0.4960
Atopy (non-atopic : atopic)**	2 : 23	4 : 23	0.7383
Oral corticosteroid use in past year (%)	42.9	27.6	0.2143
FEV_1 (% predicted)*	80.78 (74.52 to 87.03)	78.93 (72.48 to 85.38)	0.6760
Reliever use (puffs/day)*	2.94 (2.09 to 3.79)	3.09 (2.22 to 3.95)	0.8066
AQLQ*‡	0.77 (0.57 to 0.96)	0.54 (0.43 to 0.65)	0.0417
ACQ-7*¶	1.46 (1.22 to 1.70)	1.37 (1.16 to 1.58)	0.5653
Daytime symptom intensity score†§	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.7251

FEV_1, forced expiratory volume in 1 second; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire.
*Mean (95% CI).
†Median (IQR).
‡Range (best–worst): 0–4;
¶Range (best–worst): 0–6;
§Range (none–severe): 1–5
**Atopic was defined as a positive skin prick test using the following criteria: length×width any allergen from a standard panel ⩾ length×width saline *and* ⩾ 3*3.

ables before and after PEF monitoring for clinic measurements (week 12 *v* week 14, week 28 *v* week 30), and with and without PEF monitoring for diary variables. Outcomes were compared using unpaired (two sample) *t* tests adjusted for baseline and paired *t* tests for normally distributed data, and by Mann-Whitney U and Wilcoxon tests for non-parametric data. Because the ACQ includes a question about reliever use, questions 1–6 (ACQ-6: lung function data removed) and questions 1–5 (ACQ-5: lung function and reliever data removed) were also analysed.[11]

The sample size of 50 subjects was calculated based on detecting a clinically meaningful difference (0.5) in AQLQ score between groups with 80% power ($\alpha = 0.05$). To detect a 0.5 change in symptom score (80% power, $\alpha = 0.05$), a total sample size of 80 was required.

RESULTS

Fifty seven subjects were randomised (28 to group A and 29 to group B). Nine subjects (five from group A and four from group B) withdrew before completion of the study (fig 2). Blinding of randomisation allocation was not broken for any subject. Baseline demographic and clinical characteristics are shown in table 2. At baseline, subjects had mild airway obstruction and used on average 3 puffs reliever/day. Asthma related quality of life was well preserved and was slightly better in group B at baseline ($p = 0.0417$). There were no significant differences in other variables.

During the study there was no significant difference between the groups in the self-reported time spent on routine daily exercises (group A: median 12 min/day (IQR 7–20); group B: 16 min/day (IQR 8–20); $p = 0.66$). Median overall adherence to twice daily electronic monitoring was 62%.

Primary outcome measures

Primary outcome measures are shown in table 3. At week 12 there was no significant difference between the two groups in AQLQ score ($p = 0.29$). There were small differences favouring group B in daytime symptom scores ($p = 0.0192$) and night-time symptom scores ($p = 0.0636$).

Secondary outcome measures (weeks 1–12)

Reliever use

Both groups had a dramatic reduction in reliever use commencing from week 1 after randomisation (fig 3), with no significant differences between the groups at week 12. The proportion of reliever-free days increased in both groups between baseline and week 12 (group A: median baseline 6.7%, week 12 53.5%, $p = 0.001$; group B: baseline 8.3%, week 12 55.3%, $p = 0.0001$) with no significant differences between groups ($p = 0.49$ at baseline; $p = 0.19$ at week 12).

Other variables

There was no significant difference between ACQ scores at week 12 ($p = 0.234$). However, there was a statistically significant improvement in ACQ at week 12 in group B ($p = 0.0324$) but not in group A ($p = 0.49$; see online supplement). A significant improvement in ACQ was seen for group B even when the components for β_2 agonist use and lung function were omitted (see online supplement).

There were no significant differences between groups in Patient or Physician Global Assessments at week 12, although Physician Global Assessment improved significantly for group B but not group A compared with baseline ($p = 0.0467$ and $p = 0.073$, respectively).

There was no significant difference between groups in clinic FEV_1 at week 12 ($p = 0.30$), although there was a small reduction in FEV_1 (0.084 l) by week 12 in group B ($p = 0.0359$). There were no consistent differences between the two groups at week 12 for airway responsiveness to mannitol, or for mean airway resistance before and after deep inspiration. The airway responsiveness data need to be interpreted with caution due to missing data (see online supplement).

There was no difference between the groups at week 12 in volume of deep inspiration and number of breaths per minute (see online supplement), end tidal CO_2, or route of breathing, and no significant changes in any of these measures within either group during weeks 0–12. The end tidal CO_2 and route of breathing data need to be interpreted with caution due to missing data (see online supplement).

Inhaled corticosteroid dose reduction (weeks 13–28)

ICS dose

At baseline, median daily ICS dose (BDP equivalent) was 800 µg (IQR 758–1900, n = 28) and 800 µg (500–2000, n = 29) for groups A and B, respectively ($p = 0.92$). The final ICS dose was 200 µg (100–275, n = 23) and 187.5 µg (119–250, n = 25), respectively. The mean reduction in ICS dose for those who remained in the study beyond week 13 was 50% (IQR 50–75, $p<0.0001$ compared with baseline (both groups combined, n = 48).

Table 3 Primary and secondary outcome measures: comparison between groups

Outcome measure	Baseline		Difference at week 12** end stable ICS dose (95% CI)	Difference at week 28** end ICS reduction (95% CI)	Comparison between groups (p value)		
	Group A	Group B			Base	Week 12	Week 28
AQLQ – total* ¶	0.77 (0.50)	0.54 (0.30)	0.14 (−0.13 to 0.41) *[Missing: A:3, B:2]*	0.14 (−0.11 to 0.38)	0.04	0.29	0.27
Day symptom intensity score† ¶¶	2.00 (2.00)	2.00 (2.00)	0.45 (0.09 to 0.81) *[Missing: A:2, B:2]*	0.27 (−0.21 to 0.75) *[Missing: B:3]*	0.73	0.02	0.26
Night symptom intensity score† ¶¶	2.00 (1.00)	2.00 (1.00)	0.34 (−0.02 to 0.70) *[Missing: A:2, B:3]*	0.27 (−0.14 to 0.68) *[Missing: B:4]*	0.53	0.06	0.20
Symptom free days (%)* ***	23.51 (26.83)	22.07 (30.45)	−4.25 (−14.45 to 5.96) *[Missing: A:2, B:2]*	−8.56 (−22.74 to 5.61) *[Missing: B:3]*	0.85	0.81	0.23
Reliever use (puffs/day)* ¶¶	2.94 (2.20)	3.09 (2.28)	0.51 (−0.22 to 1.23) *[Missing: A:2, B:2]*	0.005 (−0.98 to 0.99) *[Missing: B:3]*	0.81	0.17	0.99
Reliever free days (%)† ***	6.67 (42.42)	8.33 (41.67)	−4.85 (−23.90 to 14.21) *[Missing: A:2, B:2]*	1.89 (−18.49 to 22.27) *[Missing: B:3]*	0.49	0.19	0.63
ACQ-7§*	1.46 (0.61)	1.37 (0.55)	0.21 (−0.14 to 0.56) *[Missing: A:1]*	0.11 (−0.20 to 0.43)	0.57	0.23	0.47
Patient Global Assessment* ‡‡	61.32 (24.89)	66.17 (20.76)	−6.21 (−18.66 to 6.23) *[Missing: B:1]*	−4.84 (−17.49 to 7.82)	0.43	0.32	0.45
Physician Global Assessment‡‡	61.43 (15.14)	62.31 (15.89)	−1.15 (−10.25 to 7.95)	−2.37 (−10.33 to 5.60)	0.83	0.80	0.55
Lung function (FEV_1% predicted)* ††	80.78 (16.14)	78.93 (16.96)	1.94 (−1.77 to 5.64)	−2.27 (−6.02 to 1.49)	0.68	0.30	0.23
Lung function (FVC% predicted)* ††	103.09 (19.22)	101.55 (18.01)	2.41 (−3.09 to 7.91)	−0.18 (−5.51 to 5.16)	0.76	0.38	0.95
End tidal CO_2 (%)† §§	4.14 (1.90)	3.77 (1.17)	−0.20 (−1.03 to 0.24) *[Missing: A:3, B:5]*	0.28 (−0.22 to 0.91) *[Missing: A:1, B:3]*	0.71	0.37	0.26
Route of breathing (nasal/%)	16/20 (80%)	13/23 (57%)	A: 14/19 (73.68%) B: 14/21 (66.67%)	A: 14/14 (100%) B: 7/17(41.18%)	0.1936	0.3970	0.0023
			Ratios at week 12 (95% CI of ratio)**	**Ratios at week 28** (95% CI of ratio)**	**Comparison between groups (p value)**		
RDR mannitol (% fall/mg)‡	0.02 (30.16)	0.18 (1.19)	1.17 (0.69 to 1.99) *[Missing: A:12, B:16]*	0.79 (0.50 to 1.25) *[Missing: A:10, B:12]*	0.28	0.54	0.30

*Mean (SD).
†Median (IQR).
‡Geometric mean (SD).
¶Asthma Quality of Life Questionnaire; range (best–worst) 0–4.
§Complete Asthma Control Questionnaire questions 1–7; range (best–worst) 0–6.
**Differences represent Group A − Group B; ratios represent Group A/Group B.
††Measured at clinic visit.
‡‡Measured on a visual analogue scale from 0 (worst) to 100 (best).
§§Measured on a custom built device (see online supplement).
¶¶Recorded using electronic diary spirometers.
***Calculated based on data recorded on electronic diary spirometers.

Clinical outcomes after ICS dose reduction

At week 28 there was no significant difference between groups in AQLQ score, daytime or night time symptom scores, reliever use, symptom-free days, Patient or Physician Global Assessments, ACQ scores, FEV_1, mean airway resistance before and after deep inspiration, airway responsiveness to mannitol, or end tidal CO_2 adjusted for baseline (table 3). Data for mannitol challenge, route of breathing, and end tidal CO_2 were not available for all subjects at week 28 (see online supplement), and these results therefore need to be interpreted with caution. Of 31 subjects with route of breathing data, more subjects breathed nasally in group A than in group B. Stability of asthma was maintained in both treatment groups during reduction in ICS dosage. This was demonstrated by maintenance of, or improvement in, asthma outcomes at week 28 compared with week 12 (see online supplement).

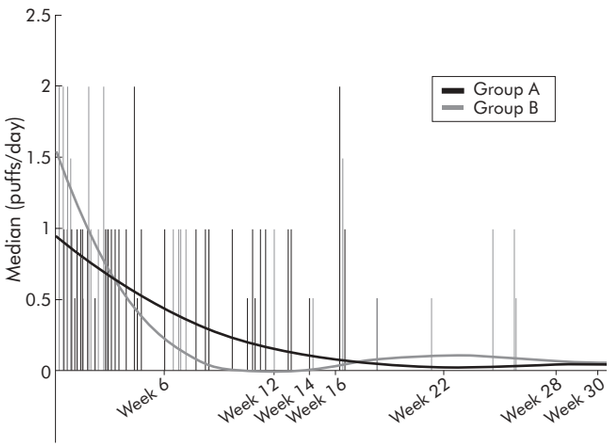

Figure 3 Reliever use reduction.

Adverse events

Twelve moderate exacerbations were experienced by 11 subjects (three in group A and eight in group B, $p = 0.11$) during the study. There were 259 other adverse events (138 in group A and 121 in group B), none of which was considered to be related to treatment. Eight adverse events (five in group A and three in group B) were attributed to mannitol (see online supplement).

Potential impact of PEF monitoring on other asthma outcomes

There were no significant differences in any outcome variables between these periods, with the exception of AQLQ in group B for week 12 *v* week 14 ($p = 0.024$) where the difference favoured the post-PEF period (see online supplement).

DISCUSSION

This study found that similar improvements in asthma symptoms, reliever use, and ICS dose were achieved in subjects with mild to moderate asthma using a technique which focused on the nasal route of breathing, hypoventilation, and breath holding, and a breathing technique incorporating non-specific upper body manoeuvres.

Importantly, these changes were achieved without impacting negatively on underlying disease control, as measured by lung function and airways responsiveness. Devising a credible control for complementary medicine interventions has been acknowledged as a difficult task,[12–15] and previous studies examining breathing exercises for asthma have used a variety of control arms including asthma education and relaxation, but this approach has limited the conclusions which can be drawn about the efficacy of the breathing technique itself. Instead, we used a second breathing technique for which there was no previous evidence of efficacy in a randomly selected asthma population, and in which there was no attempt to modulate pattern of breathing. Unlike previous studies,[16–23] we also matched all process elements of the two interventions, including the instruction about symptom relief, so that the only variable was the exercises themselves. The similarity of the improvements seen in both groups, despite the widely disparate nature of the breathing exercises they were using, suggests that the observed changes were more likely to be attributable to one or more of the shared *process* elements—such as the instruction to use the exercises initially in place of reliever for symptom relief—than to the breathing exercises themselves.

Although we found significant improvements in reliever use, some patient centred outcomes and ICS dose, there were no significant changes in physiological parameters. With one exception,[18] no previous study of breathing techniques has found an improvement in lung function[5] or airway hyperresponsiveness,[19] and there is no evidence that upper body exercises such as those used for group B would impact on lung function. Our results confirm no change in end tidal CO_2, as also reported by Bowler *et al*.[16] While data for end tidal CO_2 and mannitol challenge in the present study should be interpreted with caution due to missing data, these findings—together with the measurement of airway resistance by the forced oscillation technique—strongly suggest that the improvements observed with both breathing techniques were not measurably related to physiological changes.

It has also been suggested[6] that the failure of previous studies of breathing techniques to demonstrate improvements in lung function was due to a bronchoconstricting effect of deep breaths during PEF monitoring. However, we failed to find evidence that 2 week periods of PEF monitoring were detrimental, with even small improvements occurring in some measures. Our findings therefore suggest that breathing techniques do not mask any benefit or cause deterioration in other measures of asthma control.

Previous studies of breathing techniques have shown a trend towards a reduction in ICS dose. We found a significant and similar reduction in ICS dose in both groups, with no negative impact on other outcome measures. It is unlikely that this was due to improvement in airway inflammation, given the lack of change in indirect airway hyperresponsiveness. However, some of our subjects may have been relatively overtreated with ICS at entry, as many clinicians rely on markers such as reliever use to indicate whether a patient's ICS dose is appropriate. Further, other researchers have been able to reduce ICS doses by approximately 50% in a clinical trial setting in the absence of any other intervention.[24] Despite the lack of physiological improvement, any strategy which facilitates ICS reduction has important clinical implications and useful applications.

There are several possible mechanisms to explain the reliever reduction observed in this study. One possibility is that this effect was due to participation in a clinical trial (Hawthorne effect[25]). However, this would be an oversimplification given that reliever reduction was substantial (86% by study end) and was sustained over 8 months. For both groups there were more symptom-free days at baseline (group A: 23.5%, group B: 22.1%) than reliever-free days (group A: 6.7%, group B: 8.3%). Similar disparities have been observed in other asthma studies,[26] suggesting that patients may often use their reliever for prevention rather than actual relief of symptoms. Presumably, any instruction which defers or delays the taking of a β_2 agonist will minimise its habitual and pre-emptory use. Thus, while breathing exercises may not confer any particular physiological benefit, the process of using breathing techniques as first line symptom treatment may allow people to substantially reduce their use of β_2 agonist. This itself may be beneficial by reducing adrenergic side effects, by reducing response to allergens, or by reducing mast cell tachyphylaxis.[27–29]

Another possible explanation for the overall improvements is that the subjects recruited were a ''special'' group in terms of their personality or breathing style. No specific tests of personality, anxiety, or depression were administered. The fact that breathing exercises were mentioned in some recruitment material may have attracted subjects who were more likely to respond to the interventions, enabling both breathing techniques to function as ''very active placebos''. However, the baseline clinical characteristics of the subjects from this study, including symptom and reliever frequency, were similar to those from a more conventional clinical trial recently conducted at the same centres.[30] While it is possible that the relaxation elements of both interventions assisted in reducing anxiety and hence in reducing the perceived need for reliever, the subscores for the mood domains of the AQLQ (which includes questions about anxiety) were very low in our subjects at baseline, indicating minimal impact of anxiety and—unlike in previous studies[16 17 23]—minimal opportunity for improvement in asthma related quality of life. These subscores remained largely unchanged throughout the study, suggesting that the large reduction in β_2 agonist use was not primarily due to the relief of anxiety. There has been considerable interest in the concepts of dysfunctional breathing and hyperventilation syndrome,[31] but the clinical importance of such conditions in people with asthma has not yet been established. The Nijmegen questionnaire has been used to assess dysfunctional breathing, but was not included in the present study as there is considerable overlap with the symptoms of asthma itself. A previous study of asthmatic patients with high Nijmegen scores showed improved quality of life with a breathing technique similar to our group B intervention, but there was no reduction in reliever use or ICS dose.[23] Although some patients in the present study may have satisfied the criteria for hyperventilation, the randomisation process should have ensured that they were equally distributed between both treatment arms.

Although there was little change in AQLQ score, improvements were seen in other patient centred outcome measures including Patient Global Assessment of Control and ACQ scores. These improvements suggest that the subjects' self-efficacy was enhanced, which may have been due to a reduction in medication facilitated by breathing techniques. While the ''ideal'' study would include a group of control subjects who were instructed to withhold reliever without any substitute, gaining the agreement of subjects and the approval of an ethics committee would undoubtedly be difficult. In the present study, subjects in both groups were provided with a strategy that offered an alternative to reliever use which they appeared to accept as plausible and credible. We suggest that the combination of these factors enabled patients to reduce their reliever use in the absence of any other change.

In summary, this study shows that two completely different types of breathing techniques, taught by video,

can lead to a similar level of improvement in asthma outcomes particularly those relating to the use of a short acting β_2 agonist. These improvements are of a magnitude similar to that observed in conventional clinical trials which assess pharmacological interventions to improve asthma control, and are therefore clinically important. The improvement observed was substantial and sustained, but was not associated with a measurable effect on physiological parameters of airway inflammation. Given the magnitude of the differences in content of the two breathing techniques which were used in the present study, it appears likely that the observed clinical improvements were not due to the use of a particular type of exercise but to the *process* of both routine and as-required exercises that reinforce a message of relaxation and self-efficacy and provide a deferral strategy for β_2 agonist use. Breathing techniques may be useful in the management of patients with mild asthma symptoms who use reliever frequently, but at present there is no evidence to favour shallow breathing techniques over non-specific upper body manoeuvres.

ACKNOWLEDGEMENTS

The authors acknowledge the valuable assistance of Associate Professor Guy B Marks for additional statistical advice, Ms Karen Symons, Ms Susan Forrest-Blythe and Ms Caroline Reddel for assisting with data collection, Dr Ciça Santos (unblinded medical officer), Mr Nathan Brown, Mr Phillip Munoz and Dr Cheryl Salome for assistance with the forced oscillation technique, Dr John Brannan and Dr Sandy Anderson for assistance with the mannitol challenge, Mr Gunnar Ungar and Mr Tom Li for devising and constructing the CO_2-ROB headset, Mr Aneal Chandra for devising the analysis software for CO_2-ROB data, and Dr Jenny Alison for advice regarding the Group B exercises.

Further details are given in the online supplement available at http://www.thoraxjnl.com/supplemental.

Authors' affiliations

C A Slader, Co-operative Research Centre for Asthma, University of Sydney, and Faculty of Pharmacy, University of Sydney, Australia
H K Reddel, E G Belousova, C R Jenkins, Co-operative Research Centre for Asthma, University of Sydney, and Woolcock Institute of Medical Research, Camperdown, Australia
L M Spencer, Department of Physiotherapy, Royal Prince Alfred Hospital, Camperdown, Australia
C L Armour, S Z Bosnic-Anticevich, University of Sydney, Sydney, Australia
F C K Thien, Co-operative Research Centre for Asthma, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, and Monash University, Melbourne, Australia

This study was conducted under the auspices of the Cooperative Research Centre for Asthma, jointly funded by the Australian Federal Government and industry, including AstraZeneca, Aventis Pharma, and GlaxoSmithKline. HR was funded by the Asthma Foundation of New South Wales. CS was funded by the Australian Government Department of Education, Science and Training via an Australian Postgraduate Award.

Competing interests: none.

REFERENCES

1 **Ernst E**. Complementary therapies for asthma: what patients use. *J Asthma* 1998;**35**:667–71.
2 **Ernst E**. Use of complementary therapies in childhood asthma. *Pediatr Asthma Allergy Immunol* 1998;**12**:29–32.
3 **Shenfield G**, Lim E, Allen H. Survey of the use of complementary medicines and therapies in children with asthma. *J Paediatr Child Health* 2000;**38**:252–7.
4 **Partridge MR**, Dockrell M, Smith NM. The use of complementary medicines by those with asthma. *Respir Med* 2003;**97**:436–8.
5 **Holloway E**, Ram F. Breathing exercises for asthma. *Cochrane Database Syst Rev* 2004;**3**.
6 **Kolb P**. In: *Buteyko guide for doctors*, Buteyko Natural Therapy, 2004.
7 **Salome C**, Thorpe C, Diba C, *et al*. Airway re-narrowing following deep inspiration in asthmatic and nonasthmatic subjects. *Eur Respir J* 2003;**22**:62–8.
8 **Brannan J**, Koskela H, Anderson S, *et al*. Responsiveness to mannitol in asthmatic subjects with exercise- and hyperventilation-induced asthma. *Am J Respir Crit Care Med* 1998;**158**:1120–6.
9 **Juniper E**, O'Byrne P, Guyatt G, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;**14**:902–7.
10 **Marks G**, Dunn S, Woolcock A. A scale for the measurement of quality of life in adults with asthma. *J Clin Epidemiol* 1992;**45**:461–72.
11 **Juniper EF**, Svensson K, Mork AC, *et al*. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;**99**:553–8.
12 **Margolin M**, Avants S, Kleber H. Investigating alternative medicine therapies in randomized controlled trials. *JAMA* 1998;**280**:1626–8.
13 **Nahin R**, Straus S. Research into complementary and alternative medicine: problems and potential. *BMJ* 2001;**322**:161–4.
14 **Lane D**, Lane T. Alternative and complementary medicine for asthma. *Thorax* 1991;**46**:787–97.
15 **Paterson C**, Dieppe P. Characteristics and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ* 2005;**330**:1202–5.
16 **Bowler SD**, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial. *Med J Aust* 1998;**169**:575–8.
17 **Opat A**, Cohen M, Bailey M et al. A clinical trial of the Buteyko breathing technique in asthma as taught by a video. *J Asthma* 2000;**37**:557–64.
18 **Nagarathna R**, Nagendra H. Yoga for bronchial asthma: a controlled study. *BMJ* 1985;**291**:1077–9.
19 **Cooper S**, Oborne J, Harrison V, *et al*. Effects of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. *Thorax* 2003;**58**:674–9.
20 **McHugh P**, Aitcheson F, Duncan B, *et al*. Buteyko breathing technique for asthma: an effective intervention. *NZ Med J* 2003;**116**:710–6.
21 **Vedanthan PK**, Kesavalu LN, Murthy KC, *et al*. Clinical study of yoga techniques in university students with asthma: a controlled study. *Allergy Asthma Proc* 1998;**19**:3–9.
22 **Girodo M**, Ekstrand K, Metivier G. Deep diaphragmatic breathing: rehabilitation exercises for the asthmatic patient. *Arch Physiol Med Rehabil* 1992;**73**:717–20.
23 **Thomas M**, McKinley R, Freeman E, *et al*. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003;**58**:110–5.
24 **Hawkins G**, McMahon A, Twaddle S, *et al*. Stepping down inhaled corticosteroids in asthma: a randomised controlled trial. *BMJ* 2003;**326**:1115–20.
25 **Mayo E**. The Hawthorne Experiment. Western Electric Company. In: The human problems of an industrial civilisation, MacMillan, 1933:55–76.
26 **O'Byrne P**, Bisgaard H, Goddard P, *et al*. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;**171**:129–36.
27 **Sears M**, Taylor D, Print C, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;**336**:1391–6.
28 **Sears M**, Lotvall J. Past, present and future: β_2-adrenoceptor agonists in asthma management. *Respir Med* 2005;**99**:152–70.
29 **Taylor D**, Sears M. Regular beta-adrenergic agonists: evidence, not reassurance, is what is needed. *Chest* 1994;**106**:552–9.
30 **Jenkins C**, Thien FC, Wheatley J, *et al*. Traditional and patient-centred outcomes with three classes of asthma medication. *Eur Respir J* 2005;**26**:36–44.
31 **Thomas M**, McKinley R, Freeman E, *et al*. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001;**322**:1098–100.

Double blind randomised controlled trial of two different breathing techniques in the management of asthma

Cassandra A Slader, Helen K Reddel, Lissa M Spencer, Elena G Belousova, Carol L Armour, Sinthia Z Bosnic-Anticevich, Francis C K Thien, Christine R Jenkins

Methods

Subjects

The study was described to potential subjects as comparing two breathing techniques potentially of use for people with asthma. The complete exclusion criteria were as follows: use of long-acting beta-agonists, current smoking or >10 pack-year smoking history, unstable asthma defined as requiring out of hours medical care or night waking more than once per week, asthma exacerbation or respiratory infection in previous 4♣weeks, oral corticosteroids in previous 4♣weeks, pregnancy or planned pregnancy, substantial limitation of shoulders or thoracic spine, complete nasal obstruction, prior tuition in Buteyko (established by indirect questioning).

Study design

Randomisation numbers were issued sequentially on a site-by-site basis, and the randomisation code remained concealed until the final analyses. Subjects learned and practised their exercises by video instruction (details under ‘Interventions’ and Table 1). Videos, identified by unique codes, were packaged and issued by Clinical Supplies, GlaxoSmithKline, Melbourne.

Table 1 Forced oscillation technique results: comparison between groups

Outcome measure	Baseline		Difference at week 12•: end stable ICS dose (95% CI)	Difference at week 28•: end ICS reduction (95% CI)	Comparison between groups (p-value)		
	Group A	Group B			Base	Wk 12	Wk 28
Forced Oscillation Technique: inspiratory capacity (l)*	2.13 (0.71)	2.47 (0.63)	–0.13 (–0.55 to 0.28) *[Missing: A:3, B:5]* Ratios at wk 12• (95%CI of ratio)	–0.14 (–0.51 to 0.23) *[Missing: A:1, B:3]* Ratios at wk 28• (95% CI of ratio)	0.10 Comparison between groups (p-value)	0.52	0.44
Forced Oscillation Technique: PreDI mean Rrs ($cmH_2O/l/s$)^,*	4.81 (1.63)	5.03 (1.48)	0.92 (0.71 to 1.22) *[Missing: A:3, B:5]*	0.92 (0.71 to 1.20) *[Missing: A:1, B:3]*	0.73	0.58	0.54
Forced Oscillation Technique: PostDI mean Rrs ($cmH_2O/l/s$)^,†	4.89 (1.55)	5.39 (1.64)	1.00 (0.75 to 1.34) *[Missing: A:6, B:6]*	0.90 (0.67 to 1.22) *[Missing: A:2, B:3]*	0.52	0.98	0.50
Forced Oscillation Technique: No. breaths/minute^	10.44 (1.37)	9.13 (1.38)	1.13 (0.94 to 1.37)	1.12 (0.91 to 1.36)	0.18	0.19	0.28

*Mean respiratory system resistance, Pre-Deep Inspiration

†Mean respiratory system resistance, Post-Deep Inspiration

In addition, to reviewing the subjects' exercises, the unblinded research assistant was also used to maintain blinding and safety. Subjects were reminded at each visit to avoid saying anything that would unblind study staff.

The criteria for ICS reduction at weeks 16 and 22 were: FEV_1 >70% baseline and >50% predicted, and Response Dose Ratio [RDR] mannitol ≤2×RDR mannitol at previous visit. There were three periods, each of two-weeks duration, in which subjects performed spirometry twice daily: prior to randomisation (weeks −2–0), after the first 12♣weeks on stable ICS (weeks 12–14), and at the end of the ICS down-titration period (weeks 28–30). Weeks 14–16 served to "wash-out" any potential effects of PEF monitoring before the first ICS down-titration visit.

Forced oscillation technique (FOT)

The custom built forced oscillation device (described previously by Salome *et al*[1]) delivered an oscillation frequency of 6♣Hz, and measured flow and pressure at the mouth during tidal breathing. Measurements of respiratory system resistance (Rrs) were made during approximately 1♣minute of tidal breathing, followed by a slow deep inspiration to total lung capacity (TLC) and a passive exhalation back to tidal breathing for approximately another minute. Subjects wore a nose clip and were instructed not to hold their breath at TLC. The resulting pressure and flow signals were measured and processed using custom software to calculate the Rrs, and provided six measurements of Rrs per second. The custom software automatically excluded erroneous and extreme Rrs values, which may occur if the glottis closes or the seal around the mouthpiece is lost during testing. Mean Rrs pre- and post-deep inspiration was calculated by the software as the mean of all Rrs measurements during the corresponding period of tidal breathing. Inspiratory capacity and respiratory rate were calculated by the software using the volume trace from the FOT device.

CO_2-ROB measurement

A device was designed and constructed in-house to assess route of breathing and end-tidal CO_2. The device was designed to measure the end tidal CO_2 concentration from the nose and mouth separately, as well as whether the subject was breathing primarily through the nose, the mouth or

both (mixed). A key element of the device design was to minimise its obtrusiveness, so as not to influence the subject's usual pattern of breathing. Therefore, use of a mask or insertion of prongs into the nasal cavity would have been undesirable. To the same end, subjects were not informed about the purpose of the device, and the recordings were made whilst the subject was distracted by completing the study questionnaires.

The device consisted of a headset, with a flexible arm holding two probes. The probes were positioned in front of the mouth and the nares respectively, as close as possible without touching the face. A thin, transparent sheet of plastic was positioned between the probes to minimise mixing of airflow. Thermistors were used to detect the airflow from the mouth and nose, and a continuous on-screen display allowed identification of any problems with positioning of the device. CO_2 was sampled continuously from the nose and mouth probes, and analysed in a CO_2 analyser (Datex Normocap CO_2 monitor). The output from the CO_2 analyser and the output from the amplification circuit for the thermistors were recorded directly on a computer via an analogue to digital conversion. Recordings were made for a minimum of two minutes, and twenty measurements were made per second. The device was calibrated with respect to CO_2 prior to each use.

Reliability testing was performed by five repeated measures of end tidal CO_2 on a single subject on the same day. After each measurement, the headset was removed and repositioned to simulate the use of the device on clinical trial subjects. The median end tidal CO_2 results fell within 0.3% (approximately 2♣mmHg; 0.3♣kPa) of each other.

Analysis was carried out by an investigator blinded to the subject's treatment allocation. Customised software allowed the data to be visualised as a continuous trace for quality control selection. For CO_2 analysis, a minimum threshold of 3% was selected to identify expiratory flow, based on the normal predicted values for exhaled breath in adults,[2] and the potential dilution of CO_2 between the nose/mouth and the intake port. CO_2 concentration was recorded as the median of the peak values, excluding data which lay below the threshold and data from incomplete or fragmented breaths. Route of breathing was determined from thermistor traces, being recorded as

predominantly nasal if ≥50% of breaths were from the nose and <40% of breaths were from the mouth, predominantly mouth if ≥50% breaths were from the mouth and <40% of breaths were from the nose. Subjects were classified as having mixed route of breathing when the proportion of nasal and mouth readings were both between 40–50%.

Some technical difficulties were experienced during the use of this device, which reduced the proportion of subjects with full data. Numbers of data points for each variable are indicated in Tables 3.[2, 3] The most common problems related to fragility of the headset construction, and the finding that some results which appeared acceptable during the recording phase were found to be below the CO_2 threshold.

End tidal CO_2 results from the custom-built device, which sampled exhaled breath outside the nares, were not expected to be identical with results from other methods such as mainstream/sidestream capnography. For comparison, we recorded end tidal CO_2 measurements for 20 normal (non-asthmatic, non-smoking) adults, using the same equipment and methodology as in the clinical trial. The median end tidal CO_2 value for these subjects was 4.86% (36.9♣mmHg; 4.92♣kPa), approximately 1% higher than for our asthmatic subjects (Table 3, 3.77–4.14%, n=42). Previous studies,[3, 4] have also demonstrated lower end tidal CO_2 in general asthmatic populations than non-asthmatic populations. These results suggest that our asthmatic patients were not characterised by hyperventilation to any greater extent than other, non-selected, asthmatics.

Table 3 Peak flow periods compared with non-peak flow periods

Outcome measure	**Week 12**	**Week 14**	**p-value**	**Week 28**	**Week 30**	**p-value**
AQLQ – Total§§§§,*	A:26 B:25	A:26 B:25		A:23 B:25	A:23 B:25	
Group A	0.81 (0.56–1.06)	0.78 (0.55–1.02)	0.7316	0.47 (0.32–0.63)	0.49 (0.31–0.66)	0.8145
Group B	0.56 (0.38–0.73)	0.41 (0.30–0.53)	0.0240	0.44 (0.27–0.61)	0.41 (0.26–0.57)	0.6606
Day Symp.Intensity Score*****,#	A:21 B:22	A:21 B:22		A:18 B:19	A:18 B:19	
Group A	2.00 (1.00–2.00)	1.00 (1.00–2.00)	0.0781	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.6250
Group B	1.50 (1.00–1.63)	1.00 (1.00–2.00)	0.1309	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.5625
NightSymp.IntensityScore†††††,#	A:23 B:19	A:23 B:19		A:19 B:19	A:19 B:19	
Group A	1.50 (1.00–2.00)	1.00 (1.00–2.00)	0.2754	1.00 (1.00–1.75)	1.00 (1.00–1.00)	0.3750
Group B	1.00 (1.00–1.75)	1.00 (1.00–1.00)	0.3125	1.00 (1.00–1.25)	1.00 (1.00–1.00)	0.3750
Proportion Symp.FreeDays‡‡‡‡‡,*	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	22.97 (9.94–36.00)	34.29 (21.13–47.44)	0.0919	32.43 (17.04–47.82)	45.08 (28.40–61.77)	0.1025
Group B	23.89 (10.69–37.09)	35.40 (22.46–48.35)	0.0956	32.38 (18.29–46.48)	39.48 (25.17–53.78)	0.1889
Reliever Use (puffs/day)§§§§§,*	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	1.41 (0.61–2.20)	1.00 (0.38–1.61)	0.0651	0.73 (0.24–1.22)	0.78 (0.22–1.34)	0.7274

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Group B	1.07 (0.32–1.81)	1.00 (0.43–1.57)	0.8104	1.06 (0.30–1.82)	1.23 (0.48–1.98)	0.4841
Reliever Free Days (%)******,#	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	56.73 (37.91–75.54)	59.16 (40.66–77.67)	0.5126	72.61 (54.80–90.42)	72.31 (55.42–89.19)	0.9445
Group B	68.30 (51.08–85.53)	62.89 (45.31–80.46)	0.3223	68.81 (48.62–89.00)	62.69 (42.60–82.78)	0.2287
ACQ-7††††††,*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	1.32 (1.01–1.63)	1.19 (0.91–1.47)	0.3726	1.05 (0.78–1.32)	1.01 (0.77–1.26)	0.6825
Group B	1.19 (0.85–1.53)	1.04 (0.88–1.19)	0.1630	1.05 (0.81–1.28)	1.05 (0.72–1.38)	0.9676
Pt. Global Assessment‡‡‡‡‡‡,*	A:26 B:24	A:26 B:24		A:23 B:25	A:23 B:25	
Group A	66.42 (56.50–76.35)	67.62 (60.18–75.05)	0.8098	71.70 (61.19–82.20)	76.65 (68.76–84.55)	0.1103
Group B	72.71 (63.39–82.03)	78.50 (71.57–85.43)	0.1678	75.72 (66.55–84.89)	76.36 (70.87–81.85)	0.8813
Phys. Global Assessment§§§§§§,*	A:26 B:25	A:26 B:25		A:23 B:25	A:23 B:25	
Group A	67.19 (59.42–74.97)	70.81 (64.30–77.32)	0.0967	71.78 (66.10–77.46)	73.70 (68.29–79.11)	0.3652
Group B	66.64 (60.13–73.15)	68.12 (62.58–73.66)	0.5892	72.60 (67.18–78.02)	70.68 (65.46–75.90)	0.4876
Lung Function (FEV_1 % Pr)*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	79.97 (73.70–86.25)	80.12 (74.44–85.81)	0.9091	78.01 (71.24–84.79)	77.89 (71.15–84.63)	0.8898
Group B	71.88 (66.49–77.28)	73.28 (68.49–78.08)	0.4785	75.76 (70.61–80.91)	74.76 (69.56–79.96)	0.4591

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Lung Function (FVC % Pr)*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	101.43 (94.72–108.13)	101.01 (95.84–106.18)	0.8275	98.65 (92.07–105.23)	99.02 (92.74–105.29)	0.7867
Group B	92.30 (87.03–97.58)	94.10 (88.87–99.32)	0.2598	95.44 (90.15–100.73)	95.54 (90.14–100.93)	0.9613
RDR Mannitol^	A:9 B:9	A:9 B:9		A:9 B:9	A:9 B:9	
Group A	0.23 (0.15–0.35)	0.24 (0.14–0.42)	0.7322	0.21 (0.13–0.33)	0.22 (0.14–0.39)	0.5431
Group B	0.23 (0.16–0.35)	0.22 (0.15–0.31)	0.4947	0.23 (0.13–0.37)	0.20 (0.14–0.27)	0.3554
FOT: PreDI Mean Rrs*******,^	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	4.68 (3.85–5.67)	4.49 (3.72–5.41)	0.9255	4.36 (3.61–5.26)	4.30 (3.48–5.30)	0.4736
Group B	5.04 (4.13–6.14)	5.06 (4.27–5.99)	0.8398	4.74 (3.94–5.70)	4.98 (4.07–6.10)	0.2202
FOT: PostDI MeanRrs†††††††,^	A:22 B:23	A:22 B:23		A:22 B:20	A:22 B:20	
Group A	5.00 (4.05–6.17)	4.18 (3.28–5.38)	0.0903	4.40 (3.47–5.57)	4.75 (3.72–6.06)	0.0927
Group B	4.98 (4.03–6.16)	5.34 (4.07–6.99)	0.5621	4.84 (4.01–5.82)	5.77 (4.57–7.29)	0.0009
FOT: Inspiratory Capacity*	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	2.16 (1.84–2.48)	2.13 (1.87–2.40)	0.5194	2.08 (1.79–2.36)	2.15 (1.85–2.44)	0.3086

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Group B	2.30 (2.02–2.57)	2.24 (1.96–2.52)	0.9197	2.25 (2.01–2.50)	2.20 (1.91–2.49)	0.5085
FOT: No. breaths/min^	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	11.47 (9.67–13.26)	11.89 (9.75–14.04)	0.1621	11.25 (9.33–13.16)	10.85 (8.69–13.01)	0.2626
Group B	9.96 (8.67–11.25)	9.65 (8.26–11.04)	0.3124	9.78 (8.71–10.86)	10.45 (8.79–12.11)	0.9046
End Tidal CO_2#	A:17 B:20	A:17 B:20		A:12 B:12	A:12 B:12	
Group A	3.58 (3.51–4.52)	3.91 (3.67–4.50)	0.8311	3.81 (3.40–4.41)	3.73 (3.58–3.79)	0.4688
Group B	4.02 (3.45–5.17)	3.37 (3.20–3.61)	0.1055	3.54 (3.23–3.87)	3.53 (3.18–3.95)	0.5781
Route of Breathing (% Nasal)	A:13 B:15	A:13 B:15		A:8 B:11	A:8 B:11	
Group A	8/13 (61.5)	11/13 (84.6)	0.0833	8/8 (100.0)	5/8 (62.5)	0.0833
Group B	12/15 (80.0)	7/15 (46.7)	0.0253	5/11 (45.5)	7/11 (63.6)	0.1573

*: Mean (95% CI); # : Median (IQR); ^: Geometric mean (95% CI).

§§§§: Asthma Quality of Life Questionnaire score[5], Range (best – worst): 0–5

*****: Recorded using electronic diary spirometers

†††††: Recorded using electronic diary spirometers

‡‡‡‡‡: Calculated based on data recorded on electronic diary spirometers

§§§§§: Recorded using electronic diary spirometers

******: Calculated based on data recorded on electronic diary spirometers

††††††: Asthma Control Questionnaire score[6] using the complete questionnaire – questions 1 to 7, score (best – worst): 0–6

‡‡‡‡‡‡: Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

§§§§§§: Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

*******: Mean Respiratory system resistance, Pre-deep inspiration

†††††††: Mean Respiratory system resistance, Post-deep inspiration

Mannitol challenge

Airway responsiveness to mannitol was assessed at all visits except Week –2, unless FEV_1% was 50–65% predicted (in which case it was at the Investigator's discretion), <50% predicted, or the subject had experienced an adverse event attributed to mannitol or withheld consent. Subjects who withheld consent did so as they reported finding repeated mannitol challenges unpleasant. This was particularly the case for subjects with only mild AHR, who required high doses, and as a result reported that this was associated with productive cough, unpleasant taste, throat irritation and a slow resolution of these symptoms (typically 24–48♣hours).

At week 12, 16 subjects in group A and 13 in group B consented to a mannitol challenge. At week 28, 13 subjects in each group did so.

The mannitol challenge was performed at the Investigator's discretion when FEV_1 was 50–65% predicted. Patients who did not have a mannitol challenge were still eligible for ICS reduction at the blinded Investigator's discretion, provided they were clinically stable and met the other dose reduction criteria. The response dose ratio (RDR) is an index of responsiveness, which expresses the percentage fall in FEV_1 as a proportion of the dose required to produce that fall. The greater the RDR value, the greater the airway hyperresponsiveness as a large percentage fall in FEV_1 has been achieved with a small quantity of mannitol.

The eight (Group A:5, Group B:3) adverse events attributed to mannitol included: delayed onset of chest tightness persisting for approximately 24♣hours despite normal or improved FEV_1 post-reliever administration at the end of the challenge, vomiting, migraine, and intense irritation of the throat and/or nasal passages for approximately 24♣hours post-challenge.

Patient and physician global assessment

Patient Global Assessments were completed after the ACQ and AQLQ, but prior to any other testing or staff input, in response to the prompt "Please mark on the line to indicate how well controlled you feel your asthma has been over the last two weeks." (visual analogue score, 0–100, anchored with "Very poorly controlled" and "Very well controlled"). No information was given to

subjects about the meaning of the words “asthma control”. The Physician Global Assessment was completed ≤1♣week after the visit, with the physician instructed to take into account the spirometry, ACQ, AQLQ, Patient Global Assessment, and electronic diary data. The physician assessment was likewise recorded on a visual analogue score, 0–100, anchored with “Very poorly controlled” and “Very well controlled”, in response to the prompt “Place a mark on the line to indicate how well controlled you feel this subject’s asthma has been over the past two weeks.” No further information was provided about the definition of asthma control. The Physician Global Assessments at one site were completed by one physician, and at the other site, by one of two physicians.

Symptom free and reliever free days

Symptom free and reliever free days were calculated from the electronic data recorded using electronic diary spirometers (AM2, Erich Jaeger GmbH, Hoechberg, Germany).

Handling of missing data

Missing data were handled according to the following rules, stipulated in the protocol:

- A. Data for all subjects who were randomised into the study were analysed at week 12. For subjects who withdrew between randomisation (week 0) and week 12, the last valid observation was carried forward to week 12.
- B. At week 28, all subjects who were still participating in the study at week 13 were analysed.

Thus, for subjects still participating in the study who did not provide data at week 12 or week 28, data for these subjects were not analysed. A sensitivity analysis was conducted for the primary outcome variables and for RDR mannitol (last available observation carried forward for subjects still participating in the study in addition to carrying forward for discontinued subjects; and no data carried forward for any subject), which confirmed that the conclusions for these outcomes remained unchanged.

Results

Table 2 Primary and secondary outcome measures: comparison within groups

				Comparison within groups (p-value)		
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Base Vs Wk 12	Base Vs Wk 28	Wk 12 Vs Wk 28
AQLQ – total‡,*	A:28 B:29	A:25 B:27	A:23 B:25			
Group A	0.77(0.57–0.96)	0.80 (0.52–1.07)	0.60(0.39–0.81)	0.4922	0.4602	0.0143
Group B	0.54(0.43–0.65)	0.52 (0.34–0.70)	0.44(0.27–0.62)	0.7691	0.0773	0.1817
Day Symp. Intensity Score§,#	A:27 B:29	A:26 B:26	A:23 B:22			
Group A	2.00 (1.00–3.00)	2.00(1.13–2.25)	1.00(1.00–2.00)	0.3804	0.3054	0.0674
Group B	2.00(1.00–3.00)	1.75(1.00–2.00)	1.00(1.00–2.00)	0.0910	0.0256	0.0781
Night Symp. Intensity Score**,#	A:28 B:29	A:26 B:26	A:23 B:21			
Group A	2.00(1.00–2.00)	1.00(1.00–2.00)	1.00(1.00–1.50)	0.9217	0.3054	0.2188
Group B	2.00(1.00–2.00)	1.00(1.00–1.25)	1.00(1.00–1.00)	0.0023	0.0005	0.5625
Proportion Symp. Free Days††,*	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	23.51(13.10–33.91)	19.57 (10.40–28.74)	27.90 (16.26–39.54)	0.3695	0.7319	0.0333
Group B	22.07(10.49–33.66)	21.07 (12.09–30.05)	34.06 (22.18–45.94)	0.5146	0.0291	0.0509

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Reliever Use (puffs/day)‡‡,*	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	2.94 (2.09–3.79)	1.57(0.81–2.32)	1.12(0.41–1.83)	0.0002	<0.0001	0.1493
Group B	3.09 (2.22–3.95)	1.22 (0.58–1.86)	1.30(0.39–2.22)	<0.0001	0.0022	0.8819
Reliever Free Days (%)§§,#	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	6.67 (0.00–42.42)	53.49 (33.83–83.61)	73.75 (61.23–93.54)	0.001	0.0003	0.2979
Group B	8.33 (0.00–41.67)	55.26 (15.63–83.97)	85.24 (46.51–93.47)	0.0001	0.0002	0.7615
ACQ-7***,*	A:28 B:29	A:27 B:29	A:23 B:25			
Group A	1.46(1.22–1.70)	1.34(1.03–1.65)	1.08(0.80–1.37)	0.4851	0.0056	0.0831
Group B	1.37(1.16–1.58)	1.09(0.82–1.36)	1.05(0.77–1.32)	0.0324	0.0014	0.3216
ACQ-6†††,*	A:28 B:29	A:27 B:29	A:23 B:25			
Group A	1.30(1.04–1.57)	1.14(0.80–1.49)	0.85(0.56–1.15)	0.3946	0.0021	0.0570
Group B	1.16 (0.95–1.37)	0.78(0.51–1.05)	0.73(0.39–1.06)	0.0049	0.0018	0.5644
ACQ-5‡‡‡,*	A:28 B:29	A:27 B:29	A:23 B:25			

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group A	1.26(0.98–1.54)	1.19(0.83–1.54)	0.88(0.58–1.18)	0.7925	0.0100	0.0655
Group B	1.10(0.89–1.31)	0.79(0.50–1.09)	0.74(0.40–1.08)	0.0365	0.0091	0.5243
Patient Global Assessment§§§,*	A:28 B:29	A:28 B:28	A:23 B:25			
Group A	61.32(51.67–70.97)	67.32(57.68–76.97)	70.89(61.50–80.27)	0.2941	0.1822	0.4401
Group B	66.17(58.28–74.07)	73.54(65.22–81.85)	75.72(66.78–84.66)	0.1269	0.0353	0.5646
Physician Global Assessment****,*	A:28 B:29	A:28 B:29	A:23 B:25			
Group A	61.43(55.56–67.30)	67.57(60.67–74.47)	70.23(64.47–75.99)	0.0733	0.0159	0.3066
Group B	62.31(56.27–68.36)	68.72(62.45–74.99)	72.60(66.81–78.39)	0.0467	0.0004	0.0098
Lung Function (FEV_1 % Pr)*	A:28 B:29	A:28 B:29	A:23 B:25			
Group A	80.78(74.52–87.03)	79.69(73.39–85.99)	78.80(71.73–85.87)	0.3857	0.0633	0.4379
Group B	78.93(72.48–85.38)	75.96(68.85–83.07)	75.76(68.93–82.59)	0.0359	0.8555	0.1097
Lung Function (FVC % Pr)*	A:28 B:29	A:28 B:29	A: 23 B:25			

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group A	103.09(95.64–110.54)	100.59(93.98–107.21)	99.47(92.63–106.31)	0.2654	0.0274	0.3039
Group B	101.55(94.70–108.40)	96.90(89.26–104.54)	95.44(89.20–101.68)	0.0154	0.2641	0.1076
RDR Mannitol^	A:26 B:22	A:16 B:13	A:13 B:13			
Group A	0.02(–0.07–0.39)	0.14(0.06–0.24)	0.08(0.02–0.17)	0.4514	0.0329	0.0805
Group B	0.18(0.09–0.29)	0.10(0.04–0.18)	0.14(0.06–0.26)	0.5257	0.3268	0.2248
FOT: PreDI Mean Rrs††††,^	A:21 B:22	A:25 B:24	A:22 B:22			
Group A	4.81(3.85–6.00)	4.68(3.85–5.67)	4.37(3.59–5.33)	0.6063	0.5775	0.5932
Group B	5.03(4.23–5.99)	5.04(4.13–6.14)	4.74(3.94–5.70)	0.7323	0.3968	0.3689
FOT: PostDI Mean Rrs‡‡‡‡,^	A:19 B: 21	A:22 B:23	A:21 B:22			
Group A	4.90(3.95–6.05)	5.00(4.05–6.17)	4.37(3.41–5.60)	0.8570	0.0747	0.4944
Group B	5.39(4.30–6.76)	4.98(4.03–6.16)	4.84(4.02–5.83)	0.6347	0.3074	0.6798
FOT: Inspiratory Capacity*	A: 21 B:22	A:25 B:24	A:22 B:22			
Group A	2.13(1.80–2.45)	2.16(1.84–2.48)	2.11(1.82–2.40)	0.7132	0.5089	0.8187

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group B	2.47(2.19–2.75)	2.30(2.02–2.57)	2.25(2.01–2.50)	0.6840	0.8507	0.9032
FOT: No. Breaths/minute^	A:21 B:22	A:25 B:24	A:22 B:22			
Group A	10.44(9.06–12.03)	10.79(9.34–12.47)	10.58(8.91–12.56)	0.2617	0.3791	0.8715
Group B	9.13(7.91–10.55)	9.52(8.35–10.85)	9.49(8.46–10.64)	0.9630	0.7799	0.9801
End tidal CO_2#	A:20 B:22	A:17 B:20	A:12 B:11			
Group A	4.14(3.46–5.20)	3.58(3.43–4.16)	3.81(3.33–4.51)	0.3394	0.2754	0.5469
Group B	3.77(3.46–5.26)	4.02(3.46–5.15)	3.54(3.04–4.33)	0.8900	0.4131	0.1309
Route of breathing (Nasal)						
Group A	16/20 (80%)	14/19 (73.68%)	14/14 (100%)	Cochrane Q Test Statistic: p=0.3679		
Group B	13/23 (56.52%)	14/21 (66.67%)	7/17(41.18%)	Cochrane Q Test Statistic: p=0.5134		

*Mean (95% CI); #Median (IQR); ^Geometric mean (95% CI)

‡Asthma Quality of Life Questionnaire score[5], Range (best-worst): 0–4

§Recorded using electronic diary spirometers

**Recorded using electronic diary spirometers

††Calculated based on data recorded on electronic diary spirometers

‡‡Recorded using electronic diary spirometers

§§Calculated based on data recorded on electronic diary spirometers

***Asthma Control Questionnaire score[6] using the complete questionnaire – questions 1 to 7, Range (best - worst): 0–6

†††Questions 1 to 6 only: lung function data removed

‡‡‡Questions 1 to 5 only: lung function and reliever use data removed

§§§Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

****Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

††††Mean respiratory system resistance, Pre-Deep Inspiration

‡‡‡‡Mean respiratory system resistance, Post-Deep Inspiration

Table 4 Control arm interventions in previous studies

Intervention	**Instruction re reliever use**	**Study**
Asthma education alone	Not specified	Thomas *et al*[7]
Asthma education + relaxation technique	Not specified	McHugh *et al*[8]
Asthma education + relaxation technique + abdominal breathing exercises not involving hypoventilation	Use only when symptomatic	Bowler *et al*[3]
Placebo 'Pink City Lung Exerciser' device	Use only when symptomatic	Cooper *et al*[9]
Video entitled 'Nature's Landscapes' consisting of scenery with background classical music	"None of the investigators provided encouragement or guidance for patients to reduce their asthma medication."	Opat *et al*[10]
Physical exercises with normal aerobic respiratory patterns	No instruction provided	Girodo *et al*[11]
Control patients effectively 'wait listed' i.e. continued on their pre-study treatment regimen without intervention	No instruction provided	Nagarathna and Nagendra[12], Girodo *et al*[11], Vedanthan *et al*[13], Fluge *et al* (from [14])

References

1. Salome C, Thorpe C, Diba C, *et al*. Airway re-narrowing following deep inspiration in asthmatic and nonasthmatic subjects. *Eur Respir J* 2003;**22**:62–8.
2. Oh TE, ed. *Intensive care manual*, 4th ed. Butterworth-Heinemann, 1997: Appendix 3, 961.
3. Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial. *Med J Aust* 1998;**169**:575–8.
4. Osborne CA, O'Connor BJ, Lewis A, *et al*. Hyperventilation and asymptomatic chronic asthma. *Thorax* 2000;**55**:1016–22.
5. Marks G, Dunn S, Woolcock A. A scale for the measurement of quality of life in adults with asthma. *J Clin Epidemiol* 1992;**45**:461–72.
6. Juniper E, O'Byrne P, Guyatt G, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;**14**:902–7.
7. Thomas M, McKinley R, Freeman E, *et al*. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003;**58**:110–5.
8. McHugh P, Aitcheson F, Duncan B, *et al*. Buteyko Breathing Technique for asthma: an effective intervention. *NZ Med J* 2003;**116**:710–6.
9. Cooper S, Oborne J, Harrison V, *et al*. Effects of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. *Thorax* 2003;**58**:674–9.
10. Opat A, Cohen M, Bailey M, *et al*. A clinical trial of the Buteyko breathing technique in asthma as taught by a video. *J Asthma* 2000;**37**:557–64.
11. Girodo M, Ekstrand K, Metivier G. Deep diaphragmatic breathing: rehabilitation exercises for the asthmatic patient. *Arch Physiol Med Rehabil* 1992;**73**:717–20.
12. Nagarathna R, Nagendra H. Yoga for bronchial asthma: a controlled study. *BMJ* 1985;**291**:1077–9.
13. Vedanthan P, Kesavalu L, Murthy K, *et al*. Clinical study of yoga techniques in university students with asthma: a controlled study. *Allergy Asthma Proc* 1998;**19**:3–9.
14. Holloway E, Ram F. Breathing exercises for asthma. *Cochrane Database Syst Rev* 2004;**3**.