An inspiratory load enhances the antihypertensive effects of home-based training with slow deep breathing: a randomised trial

Chulee U Jones[1], Benjarat Sangthong[1,2] and Orathai Pachirat[1]

[1]*Khon Kaen University,* [2]*Rangsit University*
Thailand

Question: Can adding an inspiratory load enhance the antihypertensive effects of slow breathing training performed at home? **Design**: Randomised trial with concealed allocation. **Participants**: Thirty patients with essential hypertension Stage I or II. **Intervention**: Experimental groups performed slow deep breathing at home, either unloaded or breathing against a load of 20 cmH$_2$O using a threshold-loaded breathing device. Participants trained for 30 min, twice daily for 8 weeks. A control group continued with normal activities. **Outcome measures**: Resting blood pressure and heart rate were measured at home and in the laboratory before and after the training period. **Results**: Compared to the control group, systolic and diastolic blood pressure decreased significantly with unloaded breathing by means of 7.0 mmHg (95% CI 5.5 to 8.5) and 13.5 mmHg (95% CI 11.3 to 15.7), respectively (laboratory measures). With loaded breathing, the reductions were greater at 18.8 mmHg (95% CI 16.1 to 21.5) and 8.6 mmHg (95% CI 6.8 to 10.4), respectively. The improvement in systolic blood pressure was 5.3 mmHg (95% CI 1.0 to 9.6) greater than with unloaded breathing. Heart rate declined by 8 beats/min (95% CI 6.5 to 10.3) with unloaded breathing, and 9 beats/min (95% CI 5.6 to 12.2) with loaded breathing. Very similar measures of blood pressure and heart rate were obtained by the patients at home. **Conclusion**: Home-based training with a simple device is well tolerated by patients and produces clinically valuable reductions in blood pressure. Adding an inspiratory load of 20 cmH$_2$O enhanced the decrease in systolic blood pressure. **Trial registration**: NCT007919689. **[Jones CU, Sangthong B, Pachirat O (2010) An inspiratory load enhances the antihypertensive effects of home-based training with slow deep breathing: a randomised trial.** *Journal of Physiotherapy* **56: 179–186]**

Key words: Loaded breathing, Slow deep breathing exercise, Blood pressure, Heart rate, Therapeutic, Hypertension, Physiotherapy

Introduction

Hypertension is an important and common co-morbidity associated with stroke, diabetes mellitus, cardiac and renal disease. In developing countries the problem of hypertension is increasing as it is elsewhere in the world. Given the potential number of patients affected there is a pressing need for effective, accessible, and affordable treatments. Whole body exercise is generally recommended as a key component in the management of hypertension. While cycling, jogging, aerobic exercise, and dance may be acceptable to younger urban patients, these may not be so suitable for older, poorer, and rural patients for a variety of practical and cultural reasons. There are, however, some other promising non-pharmacological possibilities, including breathing training. Improvements in blood pressure have been seen with yoga training that emphasises slow and regular breathing (Patel and North 1975) and several studies have shown that patients who train with slow and regular breathing over a period of about eight weeks benefit from a reduction of blood pressure (Schein et al 2001, Grossman et al 2001, Rosenthal et al 2001, Elliot et al 2002, Viskoper et al 2003, Meles et al 2004). In these studies the pattern of breathing was guided by music, a metronome, or similar feedback devices, some of which are now available commercially. There is, however, some controversy in this area, since no improvements in blood pressure were seen in a recent study with a device that uses a tone to control the rate of breathing (Altena et al 2009).

We have recently developed a simple device to train the inspiratory muscles (Jones et al 2004) which was designed to be affordable and acceptable to a wide range of patients. The device may be used to regulate the pattern and depth of breathing but can also provide a load for the respiratory muscles to work against. Evidence is accumulating that resistance training, at least with moderate loads, has no adverse effects and may well result in modest reductions in blood pressure for moderately hypertensive individuals (Kelley and Kelley 2000, Cornelissen and Fagard 2005). It is possible, therefore, that a combination of deep, slow breathing and an inspiratory load may be more effective in reducing blood pressure than just regulating the pattern of breathing.

Therefore the specific research questions for this study were:

1. Does unloaded deep and slow breathing training reduce both systolic and diastolic blood pressure for people with mild to moderate essential hypertension?
2. Does combining this with an inspiratory load using a water pressure threshold loading device increase the effect?

Methods

Design

The study was a randomised trial with concealed allocation and partial blinding. Patients with essential hypertension Stage I or II were recruited from the Outpatients Department, Srinagarind Hospital, Khon Kaen, Thailand. Following an initial assessment the patients were assigned to one of three intervention groups by block randomised, concealed allocation: a control group, those training with unloaded breathing, and those training with loaded breathing (see Figure 1). One week before the study, participants visited the Cardiovascular Research Room at Khon Kaen University to familiarise themselves with the general procedures and to learn how to measure and record blood pressure and heart rate at home. The unloaded and loaded breathing groups also learnt how to use the water pressure threshold loading device and practised their allocated deep breathing technique (ie, unloaded or loaded). Measurements of resting heart rate and blood pressure were made both by the patients themselves in their home setting and by the investigators in the laboratory in the week before

the patients began training and in the week following the last training session. Statistical analysis was carried out by an investigator blinded to the identity of the intervention groups.

Participants

Patients were recruited from those routinely attending the hypertension clinic of Srinagarind Hospital and came from mixed urban and rural areas around Khon Kaen in the north east of Thailand. Inclusion criteria were: essential hypertension Stage I or II (systolic blood pressure 140–179, diastolic blood pressure 90–109 mmHg) based on recommendations of JNC-VII (Chobanian et al 2003); age 35–65 years; good understanding and communication; independent ambulation. Exclusion criteria were: secondary hypertension; respiratory disease; diabetes mellitus; cardiac, renal or cerebrovascular disease; dyslipidemia; pregnancy within the last 6 months. Medication was continued unchanged for the duration of the study (10 weeks). Recruitment was by medical staff and nurses of the Hypertension Unit of Srinagarind Hospital.
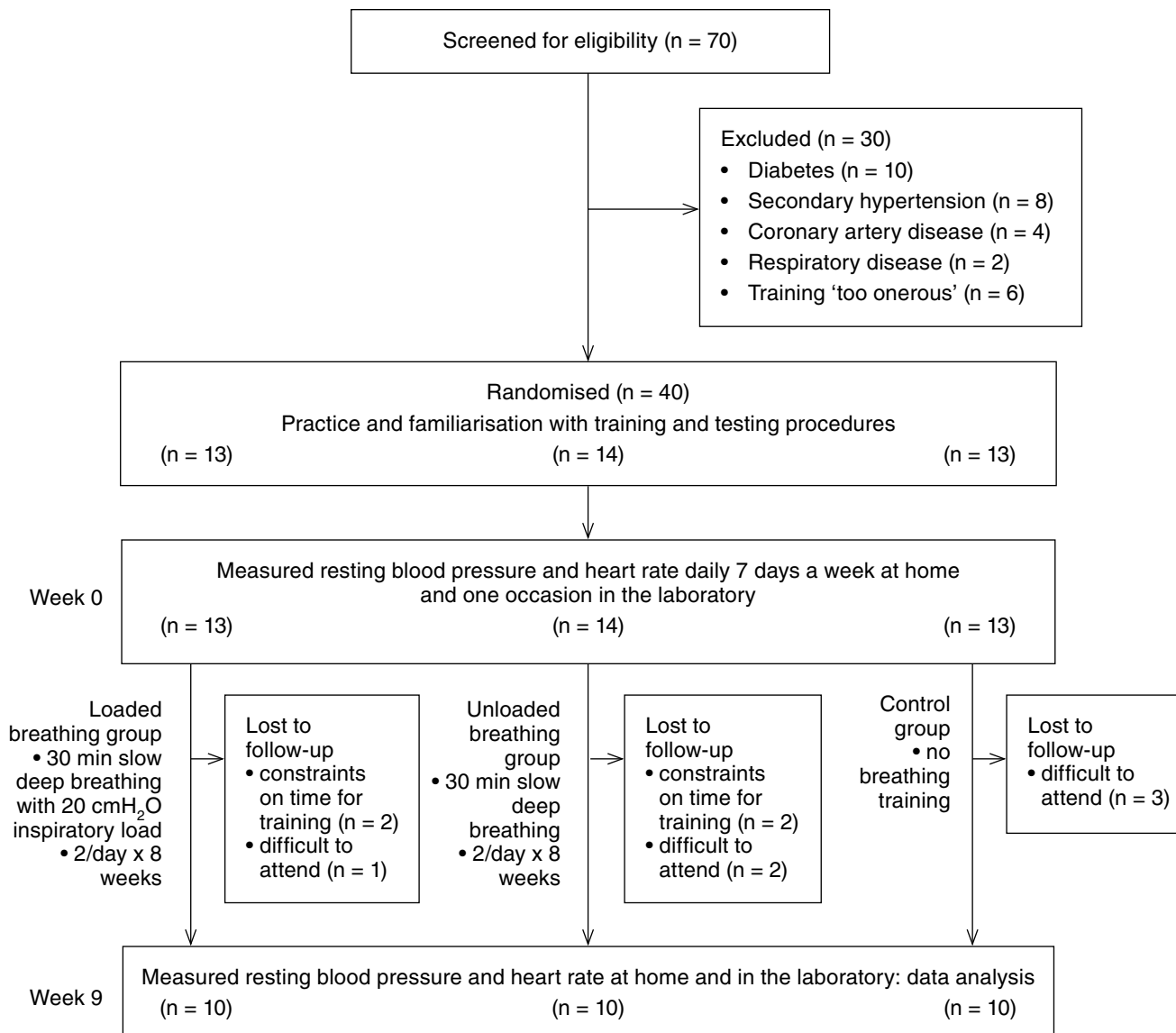

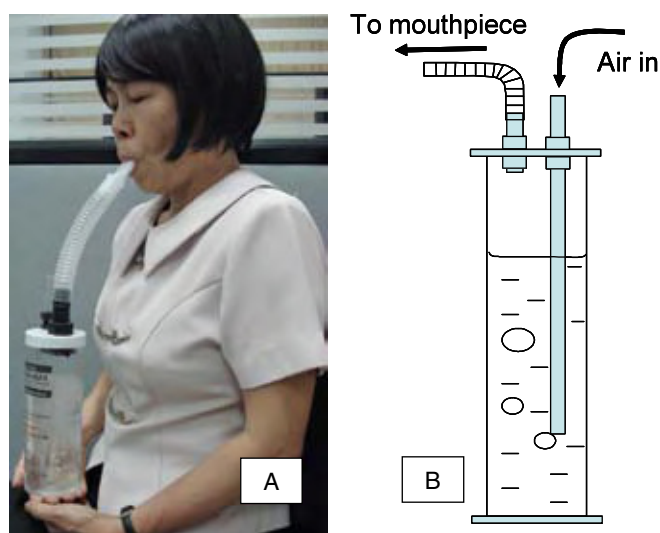**Figure 1.** Design and flow of participants through the trial.

Figure 2. The Water Pressure Threshold Bottle used for loaded breathing training. A. Using the bottle for loaded breathing. B. Diagram showing the flow of air and how the depth of the right hand tube sets the threshold inspiratory pressure.

Intervention

For training, the patients used a new simple loaded breathing device, the Water Pressure Threshold Bottle, developed in our laboratory (Figure 2). The device consists of a plastic bottle with two tubes passing through the lid. One tube provides an outlet through the top of the bottle and is connected with corrugated tube to a mouthpiece, while the other is a longer adjustable inlet tube passing into the water. The subjects breathed in through the mouthpiece and out through their nose. Thus, inspiratory resistance was determined by the column of water that was displaced, set by the length of the inlet tube below the water in the cylinder. The device is simple and easy to use and adjust. It has the added advantage that the inspired air is humidified and the bubbling sound acts as feedback helping to establish a steady breathing pattern. A preliminary study with healthy elderly subjects found no evidence of hypocapnia, no changes in blood pressure, and only a small rise in heart rate while using the device (Jones et al 2004). Participants were trained by physiotherapists from Khon Kaen University.

Training protocols: Patients in the unloaded breathing group inhaled deeply through the device with the inlet tube set just above the level of the fluid so the inspired air was humidified but there was no added resistance. For the loaded breathing group, the water level was set to provide an inspiratory load of 20 cmH$_2$0. The patients were instructed to adopt a breathing pattern with a controlled flow rate of about 200 ml/sec, an inspiratory time of 4 seconds, and a total respiratory time of 10 seconds. The paced breathing was first practised using a metronome in the laboratory until it could be reliably performed without the metronome. Patients rested for 5 seconds after every 6 deep breaths. Training was performed at home for 30 minutes, twice a day, every day for 8 weeks. Patients in the control group were asked to continue with their normal daily life.

Outcome measures

Home-based measurements: Subjects were taught to measure their blood pressure at home with a digital upper-arm blood pressure monitoring device[a]. Two measurements were made in the morning between 7.00 and 9.00 am, after at least 5 minutes rest while sitting in a comfortable chair. Subjects were asked to refrain from physical activity or caffeine for at least 30 minutes before the measurement. Resting heart rate was measured by the same device whilst the blood pressure was being measured. Data were recorded daily in the week before training and likewise in the week after the training program had ended. Two measurements were made on each day and the values averaged to give single values for that day. The measurements made on the seven days during each of these weeks were averaged to give single values pre- and post-training for each patient. Patients were contacted once a week during the training to monitor their well-being and compliance.

Laboratory-based measurements: Laboratory-based blood pressure measurements were made on one occasion in the week before training and within 3 days of the end of the training. Blood pressure was measured between 9.00 and 12.00 am with an automatic digital bedside monitor[b] after at least 15 minutes rest while sitting. Subjects were asked not to smoke or consume caffeine for 30 minutes before the measurements. The electrocardiogram was recorded with bipolar limb leads and resting heart rate calculated from averaged three consecutive R-R intervals. Two measurements were made on each occasion and the values were averaged to give single values pre- and post-training for each patient. Participants were trained by physiotherapists from Khon Kaen University.

Data analysis

We sought to detect a difference of 10 mmHg in blood pressure between groups. Assuming a standard deviation of 7.5 mmHg, 10 participants per group would provide 80% power to detect as significant, at the two-sided 5% level, a 10-mmHg difference in blood pressure between groups. To allow for loss to follow-up, the total sample size was increased to 40 participants.

Pulse pressure was taken as the difference between systolic and diastolic pressures and mean arterial pressure was calculated as diastolic blood pressure plus one-third of pulse pressure. A two-way AVOVA with *post hoc* analysis

Table 1. Baseline characteristics of participants.

Characteristic	Control (n = 10)	Unloaded (n = 10)	Loaded (n = 10)
Gender *(n male)*	3	4	4
Age *(yr)* mean (SD)	50 (5)	53 (4)	51 (5)
Weight *(kg)* mean (SD)	63 (7)	68 (12)	76 (11)
Height *(cm)* mean (SD)	156(5)	158 (10)	163 (5)
BMI *(kg/m²)* mean (SD)	27 (2)	27 (5)	29 (5)
Duration of hypertension *(yr)* mean (SD)	5.6 (2.5)	5.8 (3.4)	5.7 (2.3)
Duration of medication *(yr)* mean (SD)	4.7 (1.6)	5.1 (2.8)	4.9 (1.7)

(Tukey's test) was used to compare the mean values before and after training within groups and differences in mean changes between groups. Data are presented as means and standard deviations or 95% CIs. Statistical significance was assumed at $p \leq 0.05$. Statistical analysis was carried out by an investigator blinded to the identity of the intervention groups.

Results

Flow of participants through the trial

The flow of participants is presented in Figure 1. Of the 70 patients who volunteered, 40 were included in the trial after the initial screening. Of the 40 patients initially accepted

into the trial, 10 dropped out very early in the training for a variety of reasons, mainly because of difficulty attending the laboratory or finding the time to train. Details of the participants completing the study are given in Table 1. All participants in all groups were taking one or two of the following medications: enalapril, atenolol, or hydrochorothiazide.

Compliance with the trial method

No participants withdrew, or were withdrawn, for medical reasons or difficulty with the training. The 30 patients who completed the full 10 weeks of the study showed excellent compliance (95%) with the training and data recording. The participants commented that the training, especially the
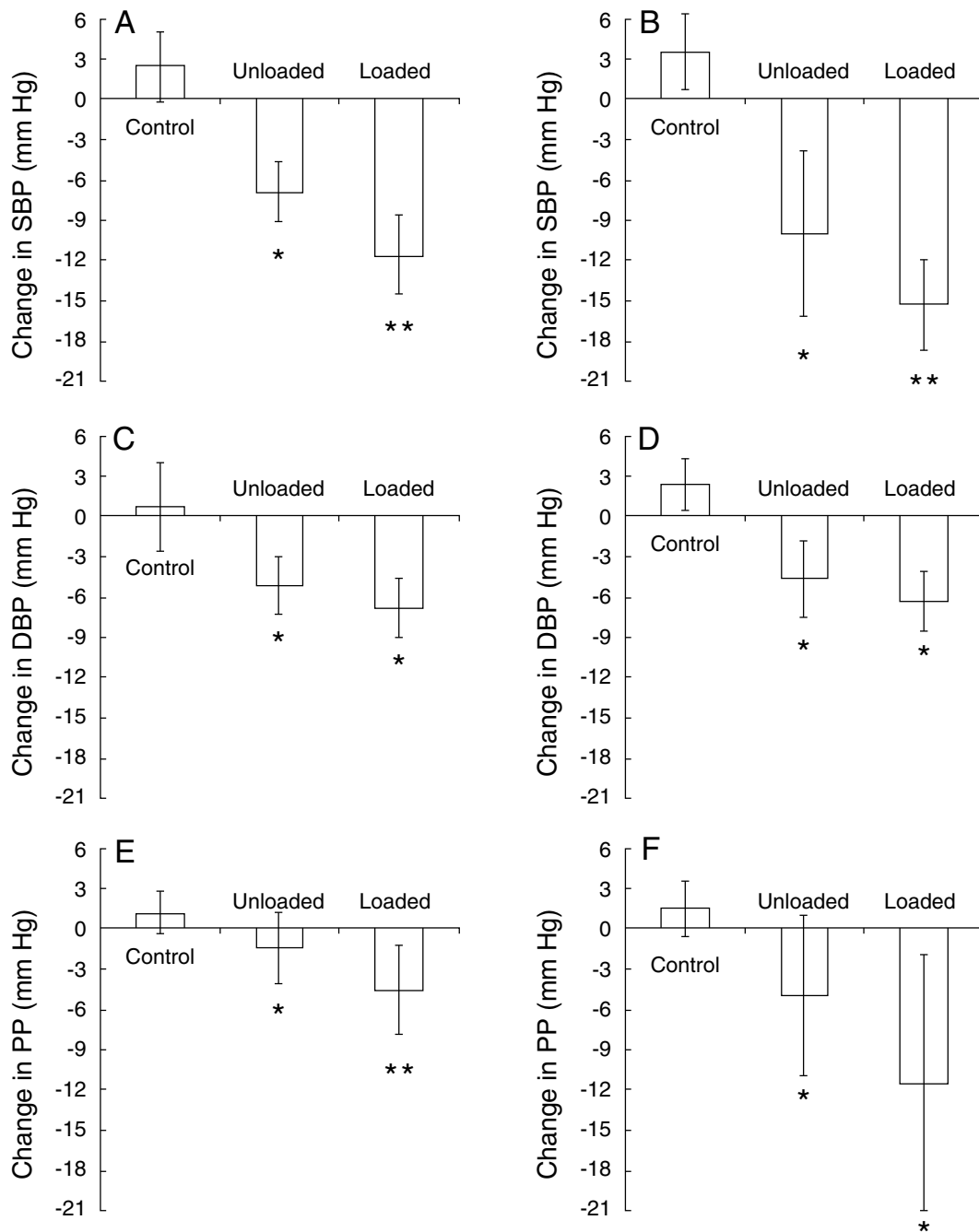

Figure 3. Mean and SD for changes in systolic (SBP), diastolic (DBP) and pulse pressure (PP) with training. A and B systolic blood pressure changes; C and D diastolic blood pressure changes; E and F pulse pressure changes in Control participants or following eight weeks of training with either Unloaded or Loaded breathing. A , C and E, measurements made by the patients at home; B, D and F, measurements made in the laboratory. * = Values that differ significantly from the control group. ** = Values that differ from the control group and also from the unloaded training group.

Table 2. Mean (SD) for each group at Week 0 and 8, mean (SD) difference within groups, and mean (95%CI) differences between groups for all outcomes measured at home and in the laboratory.

	Groups						Difference within groups			Difference between groups		
	Week 0			Week 8			Week 8 minus Week 0			Week 8 minus Week 0		
	LB n = 10	ULB n = 10	Con n = 10	LB n = 10	ULB n = 10	Con n = 10	LB	ULB	Con	LB minus ULB	LB minus Con	ULB minus Con
SBP (mmHg)												
Home	142 (8.9)	141 (5.9)	142 (9.6)	130 (8.0)	134 (5.9)	144 (8.8)	−12 (2.9)	−7 (2.2)	2 (2.6)	−4.7 (−2.4 to −7.0)	−14.0 (−11.6 to −16.4)	−9.3 (−7.5 to −11.1)
Laboratory	137 (12.7)	136 (12.6)	131 (9.1)	122 (12.8)	126 (13.7)	135 (10.9)	−15 (3.3)	−10 (6.1)	4 (2.8)	−5.3 (−1.0 to −9.6)	−18.8 (−16.1 to −21.5)	−13.5 (−11.3 to −15.7)
DBP (mmHg)												
Home	87 (5.2)	85 (4.4)	87 (5.3)	80 (5.8)	79 (3.9)	88 (4.8)	−7 (2.1)	−5 (2.2)	1 (3.2)	−1.6 (0.3 to −3.5)	−7.5 (−5.1 to −9.9)	−5.9 (−3.8 to −8.0)
Laboratory	81 (8.8)	80 (5.5)	78 (6.5)	75 (7.6)	75 (6.7)	80 (7.3)	−6 (2.2)	−5 (2.8)	2 (1.9)	−1.6 (0.6 to −3.8)	−8.6 (−6.8 to −10.4)	−7.0 (−5.5 to −8.5)
PP (mmHg)												
Home	55 (9.4)	57 (4.9)	56 (9.8)	50 (8.1)	55 (5.4)	57 (9.2)	−5 (3.2)	−2 (2.7)	1 (1.6)	−3.1 (−0.5 to −5.7)	−5.7 (−3.5 to −7.9)	−2.6 (−1.3 to −3.9)
Laboratory	59 (14.2)	56 (13.7)	53 (9.4)	47 (14.9)	51 (12.4)	55 (10.6)	−12 (9.5)	−5 (5.9)	1 (1.9)	−6.4 (0.5 to −13.3)	−12.9 (−6.9 to −18.9)	−6.5 (−4.7 to −8.3)
MAP (mmHg)												
Home	105 (4.9)	104 (4.4)	105 (5.3)	97 (5.5)	98 (4.0)	106 (5.0)	−9 (2.2)	−6 (1.9)	1 (3.1)	−2.7 (−0.9 to −4.5)	−9.5 (−7.6 to −11.4)	−6.8 (−4.8 to −8.8)
Laboratory	101 (7.9)	99 (5.5)	95 (6.0)	90 (7.5)	92 (7.5)	98 (7.1)	−11 (6.6)	−6 (3.1)	3 (2.2)	−4.8 (−4.7 to −8.3)	−13.9 (−9.6 to −18.2)	−9.1 (−7.5 to −10.7)
Heart rate (beats/min)												
Home	75 (5.8)	74 (5.6)	73 (7.3)	69 (5.9)	69 (6.2)	76 (8.1)	−7 (3.5)	−5 (1.6)	3 (2.8)	−1 (1.4 to −3.4)	−9 (−6.4 to −12.0)	−8 (−6.3 to −10.1)
Laboratory	76 (4.2)	73 (7.3)	75 (9.6)	68 (6.2)	65 (7.1)	76 (7.6)	−8 (4.5)	−8 (1.1)	1 (2.8)	−1 (2.4 to −3.4)	−9 (−5.6 to −12.2)	−8 (−6.5 to −10.3)

LB = loaded breathing, ULB = unloaded breathing, Con = control groups, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, MAP = mean arterial pressure

loaded breathing, was hard work but perfectly acceptable. Blood pressure and heart rate measures were made both by the participants themselves whilst at home and by the investigators when participants visited the laboratory. There was good agreement between these two sets of measurements, with similar changes evident in the two data sets (Table 2).

Effect of intervention

Data for the cardiovascular parameters before and after the 8-week training period are given in Table 2, together with differences within and between groups. Participants in the control group showed minimal change in any of the measured parameters. Both the training groups showed significant reductions in systolic and diastolic blood pressures of 5 to 15 mmHg (Table 2, Figure 3) with very similar changes seen in the measurements made at home by the patients and in the laboratory. The reductions in blood pressure were somewhat greater for the loaded breathing group, with the difference between the two groups reaching statistical significance for systolic blood pressure, measured either at home or in the laboratory (Table 2, Figure 3A and B). The changes in systolic blood pressure were greater than those in diastolic blood pressure with the consequence that pulse pressure was also reduced significantly when measured both at home and laboratory (Table 2, Figure 3E and F). Mean arterial pressure and resting heart rate also

fell significantly in both the unloaded and loaded training groups of patients (Table 2, Figure 4).

Discussion

Controlled slow breathing training using a relatively simple threshold loading device resulted in significant and clinically valuable reductions in systolic blood pressure, diastolic blood pressure, pulse pressure, and heart rate. Adding a resistive load to the inspiratory muscles generally enhanced the benefits, significantly so, for systolic blood pressure. These findings were replicated in home-based blood pressure monitoring by the patients and in laboratory assessments, indicating that they were not affected by the white coat' effect that can complicate the measurement of blood pressure and confuse the interpretation of trial results.

The baseline characteristics of the participants, including their medication use, were very similar between the groups, with only slightly greater height and weight in the loaded breathing group. The pre-training cardiovascular parameters were very similar in the three groups.

The threshold loading device is very suitable for home use and has the advantage that the air is humidified – avoiding the unpleasant dry mouth and throat normally associated with breathing through a mouthpiece. Such a relatively simple and inexpensive device could therefore be a valuable
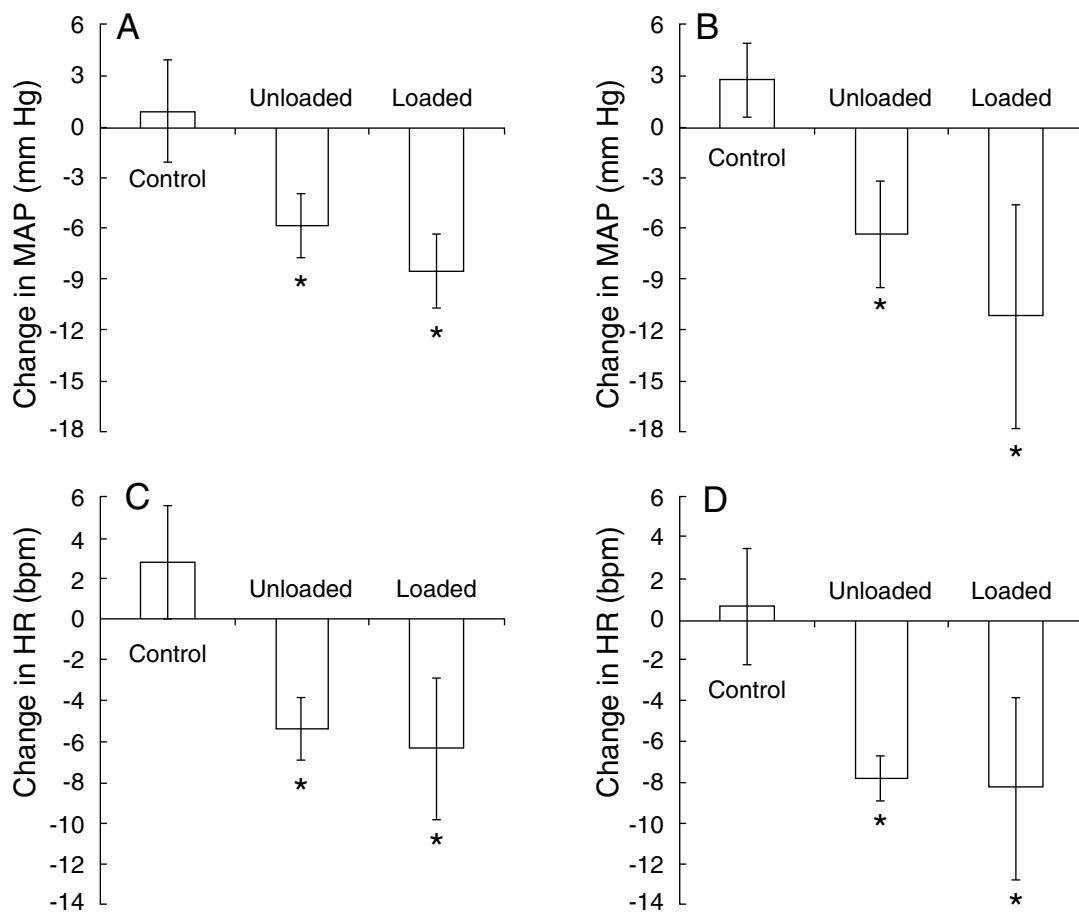

Figure 4. Mean and SD for changes in mean arterial pressure (MAP) and heart rate (HR). A and B mean arterial pressure changes; C and D resting heart rate changes in Control participants or following eight weeks of training with either Unloaded or Loaded breathing. A and C, measurements made by the patients at home; B and D, measurements made in the laboratory. * = Values that differ significantly from the control group.

adjunct to conventional approaches for treatment of hypertension in all communities.

Although participants and assessors were not blinded, participants were not informed that there were loaded and unloaded breathing groups, so this may have reduced some sources of bias due to lack of blinding on this comparison. The potential problems of an unblinded study were further minimised by the nature of the measurements since blood pressure and heart rate were recorded automatically and required no particular skill or judgments to be made either by the participants at home or the experimenters in the laboratory (Wood et al 2008). Furthermore, the post-training measurements were all made without either the participants or the experimenters having access to the pre-training data measured some eight weeks earlier.

The consequences of unloaded breathing training for systolic and diastolic blood pressure were very similar to previous reports where breathing has been regulated in various ways (Schein et al 2001, Grossman et al 2001, Rosenthal et al 2001, Elliot et al 2002, Viskoper et al 2003), with the mean changes being 6 to 10 mmHg for systolic and diastolic blood pressure for all the trials, including the present one. The reductions in blood pressure achieved in this way are clinically valuable and appreciably greater than those reported for aerobic physical training reductions of 3.8 and 2.6 mmHg for systolic and diastolic blood pressure (Whelton et al 2002) which is generally recommended as an adjunct to treatment for hypertension.

It is of particular interest that both training modes reduced systolic blood pressure and pulse pressure. Systolic blood pressure is considered a better predictor of cardiovascular complications than diastolic blood pressure (Lewington et al 2002). It has recently been suggested that systolic blood pressure should be the target of treatment in people aged over 50 years with hypertension (Williams et al 2008) but controlling systolic blood pressure with pharmacological measures is more difficult than controlling diastolic blood pressure (Waeber and Mourad 2006). Pulse pressure has been reported to be a good predictor of myocardial infarction and cardiovascular risk in hypertensive subjects (Benetos 1999) and was the only measure of blood pressure found to be significantly and independently related to the incidence of myocardial infarction in treated and untreated hypertension (Fang et al 1995). The greater reduction in systolic blood pressure using loaded breathing training in the present study indicates that this method could be a valuable adjunct treatment for older hypertensive people and in cases of isolated systolic hypertension.

Our findings differ from previous work involving breathing training in that there was a consistent reduction of 5 to 8 beats/min in resting heart rate as a result of both loaded and unloaded breathing whereas previous studies of breathing training report no change in heart rate (Schein et al 2001, Grossman et al 2001, Rosenthal et al 2001, Viskoper et al 2003). These previous studies used devices which guided the breathing rate but did not necessarily control the depth of inspiration, as is evident from the high variation in the ratio of inspiratory to expiratory times during breathing training with *RESPeRate* (Schein et al 2007). With the pressure threshold device we have used, it is necessary to maintain a certain inspiratory pressure to obtain any air flow. With

the 20-cmH$_2$O threshold the minimal airflow maintained for the 4-s inspiratory time ensured a relatively large chest expansion. This lung inflation and the negative intrathoracic pressures generated may have activated pulmonary stretch receptors and the Hering-Breuer inflation reflex, which would reduce heart rate and systemic vascular resistance.

The mechanisms by which breathing training results in reductions of blood pressure are not clear. It has been suggested that in essential hypertension there is enhanced sympathetic activity (Guzzetti et al 1988, Goldstein, 1993) pressor hyper-responsiveness (Goldstein 1993), and reduced vagal activity at rest (Guzzetti et al 1988). Since the breathing training reduced resting systolic and diastolic blood pressure together with heart rate, one mechanism of its action may be that the training increased cardiac vagal tone and reduced sympathetic activity to the cardiac and peripheral arterioles. It is known that resistive slow deep breathing at elevated tidal volumes – as in this study – leads to decreased sympathetic excitation (Seals et al 1993). Hyperventilation and low end-tidal carbon dioxide pressures at rest have been described in essential hypertension (Joseph et al 2005), which could enhance peripheral chemoreflex sensitivity (Trzebski et al 1982) and sympathetic activity. Slow breathing training may reduce hyperventilation at rest, as seen in yoga practice, thereby altering the chemoreflex sensitivity (Spicuzza et al 2000). A change in baroreflex sensitivity is another possibility as the baroreflex-cardiac sensitivity is shown to be decreased in hypertension (Goldstein 1993), and the effects of slow deep breathing reducing blood pressure have been suggested to be mediated via an increase in baroreflex sensitivity (Joseph et al 2005). Loaded breathing has also been shown to increase the aortic baroreflex as a consequence of augmented negative intrathoracic pressures (Angell-James 1971). The greater response of systolic blood pressure found with loaded slow deep breathing may be a consequence of the load amplifying some of the mechanisms discussed above.

The results presented here suggest that the key factor in reducing blood pressure is deep inspiration and lung inflation. However, one of the most common commercially available devices, *RESPeRate*, emphasises the control of expiration. It may be the case that any form of controlled slow breathing rate is sufficient to reduce diastolic blood pressure. Alternatively, although *RESPeRate* aims to control expiration, in order to be able to breathe out slowly subjects need to take a deep breath in, thus providing a degree of lung inflation. In either case it seems important to have a high level of lung inflation in order to obtain the decreases in systolic pressure that we have observed.

We conclude that controlled breathing using this novel and simple device for 8 weeks is well tolerated by patients for home-based training and provides clinically valuable reductions in blood pressure. Adding an inspiratory load of 20 cmH$_2$O enhanced the decrease in systolic blood pressure, an important target for the reduction of cardiovascular risk in people with hypertension. For such training to be widely used, however, further studies will be required to determine the minimum duration and intensity of training needed to produce useful changes and how long the effects last after the end of training so that the frequency with which patients need to train can be determined. ■

Correspondence: Dr Chulee U Jones, Assistant Professor, Department of Physical Therapy, Khon Kaen University, Thailand. Email: chulee kku.ac.th

References

Altena MR, Kleefstra N, Logtenberg SJ, Groenier KH, Houweling ST, Bilo HJ (2009) Effect of device–guided breathing exercises on blood pressure in patients with hypertension: a randomized controlled trial. *Blood Pressure* 18: 273–279.

Angell-James JE (1971). The effects of changes in extramural, 'intrathoracic' pressure on aortic arch baroreceptors. *Journal of Physiology (London)* 214: 89–103

Benetos A (1999) Pulse pressure and cardiovascular risk. *Journal of Hypertension* 17: s21–s24.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izza JL, et al (2003) The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Journal of American Medical Association* 289: 2560–2572.

Cornelissen VA, Fagard RH (2005) Effect of resistance training on resting blood pressure: a meta analysis of randomized controlled trials. *Journal of Hypertension* 23: 251–259.

Elliott W, Izzo JL, Rosing D, Synder C, White WB, Alter A (2002) Hypertension reduction by device–guided breathing shows a dose–response relationship. *American Journal of Hypertension* 22: s116.

Fang J, Madhaven S, Cohen H, Alderman MH (1995) Measures of blood pressure and myocardial infarction in treated hypertensive patients. *Journal of Hypertension* 13: 413–419.

Giannattasio C, Failla M, Meles E, Gentile G, Grappiolo A, Mancia G (2002) Efficacy of self treatment of hypertension at home with device-guided breathing. *American Journal of Hypertension* 15: 186A.

Goldstein DS (1983) Arterial baroreflex sensitivity, plasma catercholamines and pressor responsiveness in essential hypertension. *Circulation* 68: 234–240.

Grossman E, Grossman A, Schein MH, Zimlichman R, Gavish B (2001) Breathing-control lowers blood pressure. *Journal of Human Hypertension* 15: 263–269.

Jones C, Pongsuwan P, Khrisanapant W, Bunsawat W (2004) Cardiopulmonary responses in the elderly during inspiratory muscle loading. *European Respiratory Journal* 24: 243s.

Joseph CN, Porta C, Casucci G, Casiraghi N, Maffeis M, Rossi M, et al (2005) Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. *Hypertension* 46: 714–718.

Kelley GA, Kelley KS (2000) Progressive resistance exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 35: 838–843.

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360: 1903–1913.

Meles E, Giannattasio C, Failla M, Gentile G, Capra A, Mancia G (2004) Non-pharmacologic treatment of hypertension by respiratory exercise in the home setting. *American Journal of Hypertension* 17: 370–374.

Patel C, North W (1975) Randomized controlled trial of yoga and biofeedback in management of hypertension. *Lancet* 19: 93–95.

Rosenthal T, Alter, Peleg E, Gavish B (2001) Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. *American Journal of Hypertension* 14: 74–76.

Schein MH, Gavish B, Herz M, Rosner-Kahana D, Naveh P, Knishkowy B (2001) Treating hypertension with a device that slows and regularises breathing: a randomised, double-blind controlled study. *Journal of Human Hypertension* 15: 271–278.

Schein MH, Alter A, Levine S, Baeysky T, Nessing A, Gavish B (2007) High blood pressure reduction in diabetics with interactive device-guided paced breathing: final results of a randomized controlled study. *Journal of Hypertension* 25: S192.

Spicuzza L, Gabutti A, Porta C, Montano N, Bernardi L (2000) Yoga and chemoreflex response to hypoxia and hypercapnia. *Lancet* 356: 1459–1496.

Trzebski A, Tafil M, Zoltowski M, Przybylski J (1982) Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension. *Cardiovascular Research* 16: 163–172.

Viskoper R, Shapira I, Priluck R, Mindlin R, Chornia L, Laszt A (2003) Nonpharmacologic treatment of resistant hypertensive by device-guided slow breathing exercises. *American Journal of Hypertension* 16: 484–487.

Waeber B, Mourad JJ (2006) Targeting systolic blood pressure: the key to controlling combined systolic/diastolic hypertension. *American Journal of Hypertension* 19: 985–986.

Whelton SP, Chin A, Xin X, He J (2002) Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Annals of Internal Medicine* 136: 493–503.

Williams B, Lindholm LH, Sever P (2008) Systolic pressure is all that matters. *Lancet* 371: 2219–2221.

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *British Medical Journal* 336: 601–605.