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Effect of Slow- and Fast-Breathing Exercises on Autonomic Functions in Patients with Essential Hypertension

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Abstract

Objectives: Breathing exercises practiced in various forms of meditations such as yoga may influence autonomic functions. This may be the basis of therapeutic benefit to hypertensive patients.
Design: The study design was a randomized, prospective, controlled clinical study using three groups.
Subjects: The subjects comprised 60 male and female patients aged 20–60 years with stage 1 essential hypertension.
Intervention: Patients were randomly and equally divided into the control and other two intervention groups, who were advised to do 3 months of slow-breathing and fast-breathing exercises, respectively. Baseline and postintervention recording of blood pressure (BP), autonomic function tests such as standing-to-lying ratio (S/L ratio), immediate heart rate response to standing (30:15 ratio), *Valsalva* ratio, heart rate variation with respiration (E/I ratio), hand-grip test, and cold presser response were done in all subjects.
Results: Slow breathing had a stronger effect than fast breathing. BP decreased longitudinally over a 3-month period with both interventions. S/L ratio, 30:15 ratio, E/I ratio, and BP response in the hand grip and cold pressor test showed significant change only in patients practicing the slow-breathing exercise.
Conclusions: Both types of breathing exercises benefit patients with hypertension. However, improvement in both the sympathetic and parasympathetic reactivity may be the mechanism that is associated in those practicing the slow-breathing exercise.

Introduction

Autonomic imbalance is one of the multifactorial causes of essential hypertension currently.[1] The side-effects, cost of antihypertensive drugs, and nonadherence to medication have led to the search for a nonpharmacological approach to control blood pressure (BP) either as an initial or adjunct treatment. Several studies and recent meta-analysis have demonstrated that lifestyle modifications such as physical exercise, salt restriction, weight reduction, relaxation and stress-relieving techniques, yoga, meditation (especially transcendental meditation), *qigong* and Zen Buddhist meditation, biofeedback, and modern practices that involve use of breathing devices are capable of lowering BP.[2–8]

One common practice in many of these therapeutic measures is the use of breathing exercises of different depth and frequency. Voluntarily controlling the breathing is likely to bring about alterations in the autonomic responses. The frequency of respiration differentially affects the cardiovascular system. Slow breathing is generally believed to decrease the basal heart rate, heart rate response to standing,[9] and BP;[10] it decreases sympathetic activity during altitude induced hypoxia,[11] leads to better oxygenation, decreases peripheral chemoreceptor function, and improves exercise performance and baroreflex function and sensitivity.[12] Slow spontaneous breathing is independently associated with low levels of central sympathetic outflow. Fast breathing, on the other hand, is known to increase the BP and the heart rate, and enhance sympathetic drive to the myocardium. This effect has been observed in normal individuals.[13] Other researchers, however, have reported no alteration in cardiovascular parameters or autonomic regulation following the practice of fast breathing.[9] Therefore, the effects of fast breathing in people with hypertension need to be thoroughly evaluated, to ensure its safety in prescribing it to these patients.

Yogic pranayama involves both slow- and fast-breathing exercises, whose therapeutic potential needs scientific explanations. Since there has been no comprehensive systematic study stating and comparing the effects of slow- and fast-breathing exercises on autonomic functions in patients with hypertension, the present study aimed to evaluate the

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efficacy and safety of these breathing exercises and also to study whether the mechanism involved an alteration of the sympathetic or parasympathetic reactivity or both.

Methods

The study was conducted in the Department of Physiology, Maulana Azad Medical College, New Delhi. It included 60 patients of either sex in the age group 20–60 years with essential hypertension attending the medical outpatient department and hypertensive clinic of Lok Nayak Hospital, New Delhi. Ethical clearance from the institute's committee was obtained prior to the initiation of the study. The patients were graded as stage 1 hypertension according to the guidelines established by the European Society of Cardiology, with the systolic BP between 140 and 159 mm Hg and diastolic BP between 90 and 99 mm Hg. Some patients were without medication, while others were receiving either diuretics or angiotensin-converting enzyme inhibitors or both as per standard treatment guidelines.[14]

Patients who were not in the age group or stage of hypertension mentioned, with normal autonomic function tests, with a history of smoking, alcohol or drug intake, receiving drugs that alter the heart rate and subjects already performing breathing or yogic exercises were excluded from the study. Similarly, patients with secondary hypertension, diabetes mellitus, chronic breathing disorders, congestive heart failure, ischemic heart disease, chronic atrial fibrillation, previous stroke, psychiatric disorder, or clinical evidence of malnutrition were not included.

Study Groups

The patients with stage 1 hypertension were equally divided in three groups, each group comprising 20 patients based on power analysis and previous studies, with or without medication.

- Group 1. Patients without intervention.
- Group 2. Patients prescribed slow-breathing exercises.
- Group 3. Patients prescribed fast-breathing exercises.

Experimental Protocol

The patients were informed that they were part of a study protocol, and informed consent was obtained. The yoga instructor and his team asked each subject to pick up one of the 60 slips (20 for each group) to allocate the group. The resident and technician involved in recording BP and autonomic functions were unaware of the type of breathing exercise practiced by the patient. The patients were advised not to discuss this with them or with other patients in the laboratory.

A health checkup, which included history, anthropometric measurements of height and weight, and a detailed general and systemic examination, was performed before the study was started. Laboratory investigations included estimation of hemoglobin, blood sugar, lipid profile, blood urea, serum creatinine, urine routine and microscopic examination, and a baseline 12-lead electrocardiogram (ECG). A baseline recording of BP and all autonomic function tests mentioned later was done.

Patients were instructed to continue with their routine lifestyle and diet without further modification and not to practice any new yogic technique or exercise other than that prescribed during the study period. Groups 2 and 3 patients were asked to come daily over a period of 2 weeks (14 working days) to learn the breathing exercise technique. Once the technique was learned, they were instructed to strictly practice the exercises for 15 minutes twice daily 10–12 hours apart, for a period of 3 months. If required, they could also use recorded cassettes and time their breathing rate or ask others to time them.

A questionnaire was given to all the patients who were asked to follow up at the clinic every month to ensure motivation and compliance. The participants were instructed that they could practice their breathing exercise any time during the day if they missed the specific time.

At the end of 3 months, BP and autonomic function tests were repeated in the same laboratory, at the same time for all patients, who were advised not to do any breathing exercise on the day of testing. All female patients were asked to come preferably in the postmenstrual period for testing. Two (2) patients did not practice slow-breathing exercises regularly and 3 could not learn the technique of fast breathing in spite of all efforts, and 2 patients started dieting. They were not discouraged from visiting the hypertension clinic or breathing exercise sessions, but their results are not included in the groups mentioned here.

Assessment of autonomic function tests

Autonomic function tests were carried out on each patient around 9 AM, at an ambient laboratory temperature between 16°C and 20°C. They were familiarized with the testing procedures to allay any apprehension or anxiety associated with the test. The patients had been instructed to come 1–2 hours after a light meal and to refrain from caffeinated drinks.

A baseline recording of various autonomic function tests was done. One (1) or more than one abnormal test was considered as an indication of autonomic dysfunction.[15] All measurements of heart rate were done from a continuous recording of ECG in lead II, and systemic arterial BP was measured from the left upper arm with patients in a sitting position using an appropriate-size cuff and zero-error mercury sphygmomanometer by auscultatory method. Baseline BP was taken in the yoga laboratory between 9 and 10 AM, after 5 minutes of rest, 1 minute apart until the last two readings did not differ by more than 10% in both systolic and diastolic BP values. The average value of these measurements represented the BP.

The following autonomic function tests were performed according to the well-validated procedures described by Bannister and Mathias.[16] Autonomic dysfunction was classified according to results of the standard battery of test.[17] These functions have been standardized in the laboratory and the results are reproducible.

Standing to lying ratio (S/L ratio)

The patient was asked to stand and then to lie on a couch without any support. A continuous ECG was recorded from 20 beats before to 60 beats after lying down. The point at which the patient started to lie down was precisely marked. S/L ratio was calculated as the ratio of longest R-R interval during the 5 beats before lying down to shortest R-R interval during 10 beats after lying down. The maximum ratio of three trials was considered. An S/L ratio of >1 was taken as normal and <1 is taken as abnormal.

Immediate heart rate response to standing (30:15 ratios)

Each patient was asked to lie supine quietly on a couch for 5 minutes with sphygmomanometer and ECG leads attached. After a basal recording of the heart rate, the patient was asked to stand up immediately, and changes in the heart rate were noted for 1–3 minutes. A point was marked on the ECG record to identify the point of standing. The 30:15 ratio was calculated by taking the ratio of R-R interval at beat 30 and at beat 15 after standing. The 30:15 ratio is normally >1.04 and considered abnormal if <1.

Valsalva *ratio*

Patients were seated comfortably with the nose clipped and a mouthpiece inserted between the teeth and lips. The other end of the mouthpiece was connected to a mercury manometer. The patient was asked to breathe forcefully into a mouthpiece and maintain an expiratory pressure of 40 mm Hg for 15 second. A continuous ECG was recorded 1 minute before the maneuver, during the maneuver, and 45 seconds following strain release. *Valsalva* ratio was taken as the ratio of longest R-R interval after the strain to the shortest R-R interval during the strain. A value >1.45 was taken as normal, between 1.20 and 1.45 as borderline, and <1.20 was considered as abnormal.[18]

Heart rate variation with respiration (E/I ratio)

Resting heart rate was recorded and then the patient was asked to breathe deeply at a rate of six breaths per minute, allowing 5 seconds each of inspiration and expiration. The expiratory to inspiratory heart rate ratio was calculated as the sum of the six longest R-R intervals divided by the sum of the six shortest R-R intervals. Values were compared to normal age-related values.[19]

Hand grip test

The patients held the hand grip dynamometer in the dominant hand, compressing it with maximum effort, and the tension generated was noted. The maximum of the three efforts with a 1-minute interval between each was considered as maximum isometric tension (T max). The patient was then asked to maintain a pressure equivalent to 30% of T max for 5 minutes. BP was recorded after every 30 seconds from the nonexercising arm. The rise in diastolic BP just before the release of grip was taken as the index of sympathetic response. Diastolic BP >15 mm Hg was considered as normal, 11–15 mm Hg as borderline, and <10 mm Hg as abnormal.[20]

Cold pressor response

This was the last of the series of tests performed. One (1) hand of the patient was immersed in cold water at 4°C–6°C. BP was recorded from the other arm before the procedure was started (baseline) and at 30-second intervals for a period of 2 minutes. Maximum increase in the systolic and diastolic pressure during the test procedure was noted. The rise in systolic BP >15 mm Hg and diastolic BP >10 mm Hg was considered as normal.[21]

Experimental protocol for slow- and fast-breathing exercise

Patients were called in groups of 4–6, daily at 9 AM, in a well-ventilated room specially designated for the study with an ambient room temperature maintained at 16°C–20°C, in the Department of Physiology of Maulana Azad Medical College. They were made to sit comfortably on the floor in yogic padmasana position to relax for about 5 minutes. The breathing exercise was demonstrated daily for the first few days until the technique to achieve the desired rate was learned, perfected, and confirmed by a yogic instructor. Subsequently, the patients performed the exercises themselves and the technique was checked on subsequent visits to the department.

Slow-breathing exercise technique[9]

The patient was first asked to close one nostril with a thumb and slowly breathe in completely through the other for 6 seconds. This nostril was then closed and the patient exhaled through the other nostril over a period of 6 seconds. These steps completed one breathing cycle. An attempt was made to keep the breathing rate about 5–6 breaths per minute. Such alternate nostril breathing cycles were repeated continuously for a period of about 15 minutes in one sitting. Alternate nostril breathing was chosen because breathing through a particular nostril can affect autonomic functions. Right nostril breathing increases sympathetic activity while left nostril breathing decreases it.[22–25]

Fast-breathing exercise technique[9]

Patients were instructed to breathe quickly and deeply, with an inhalation and exhalation time of 1 second each for 1 minute, following which they were given 3 minutes of rest. The procedure was repeated 4 to 5 times over a period of 15 minutes.

Statistical Analysis

The study outcomes were the average weight, systolic and diastolic BP changes, heart rate, and BP changes in response to various autonomic function tests. The change in all variables at baseline and at 3 months postintervention was evaluated using analysis of variance (ANOVA). Having established this variation, ANOVA for repeated measures was done for each group within and between subjects to see the change of 3 months intervention from baseline. In addition, the intergroup variation was assessed by using unpaired t test. The difference within the group was assessed with the help of paired t test. Pearson's χ^2 test was done to see whether the three groups varied in terms of gender representation.

Results

Patient characteristics

The three groups of patients with essential hypertension were comparable and balanced in terms of height, weight, and body mass index. There was no difference in the groups

Table 1. Physical Characteristics and Details of Antihypertensive Therapy in the Three Groups of Patients

Parameters	*Group 1* (n = *20)*	*Group 2* (n = *20)*	*Group 3* (n = *20)*
Gender (male/female)	12/8	10/10	9/11
Height (cm)	158.80 ± 5.28	161.95 ± 5.34	158.10 ± 7.12
Weight (kg)	63.15 ± 6.94	63.90 ± 6.83	62.40 ± 7.74
Weight after 3 months (kg)	62.80 ± 6.72	63.80 ± 6.61	61.40 ± 7.23
BMI (kg/m^2)	24.8 ± 2.10	24.3 ± 1.41	24.8 ± 1.64
BMI after 3 month (kg/m^2)	24.7 ± 2.07	24.3 ± 1.38	24.5 ± 1.58
Number of patients on ACE inhibitors	10	8	4
Number of patients on diuretics	10	2	4
Number of patients on ACE inhibitors plus diuretics	0	2	4

Result represents data of subjects who completed the study. All values are mean ± standard deviation. Comparison of baseline and postintervention; $^*p < 0.05$ is significant. No significant difference was observed.

BMI, body–mass index; ACE, angiotensin-converting enzyme inhibitor.

based on gender ($p = 0.627$). All patients in group 1, and 60% of patients in each of the other two groups were on antihypertensive therapy (Table 1). For the others, breathing exercises were the only form of intervention.

Baseline BP and autonomic functions

One-way ANOVA showed no difference in baseline systolic and diastolic BP in the three groups ($p = 0.725$, 0.899, respectively) (Figs. 1 and 2). Intergroup comparison using unpaired *t* test confirmed this ($p = 0.804$, 0.766, and 0.634 for systolic and $p = 0.882$, 0.760, and 0.653 for diastolic BP between groups 1 and 2, 1 and 3, and 2 and 3, respectively). S/L ratio and 30:15 ratios in groups 1 and 2, E/I ratio in groups 2 and 3, and BP response to hand grip test (HGT) and cold pressor response (CPR) in all three groups was lower than normal values. *Valsalva* ratio was normal in all three groups. Baseline autonomic differences existed among the three groups ($p = 0.000$ in S/L ratio, 0.009 in 30:15 ratio, 0.022 for HGT, $p = 0.020$ for systolic BP of CPR as shown by ANOVA and supported by *t* test in Table 2).

Effects of treatment and breathing exercises on BP and autonomic functions (intergroup comparisons)

One-way ANOVA showed a significant change between groups for both BP and autonomic functions ($p = 0.000$ for all except $p = 0.005$ for *Valsalva* response).

Intergroup differences in autonomic function test (after treatment and breathing exercises) were seen (Table 2). In all groups, between-subjects change from baseline to 3-month intervention was significant ($p = 0.000$ each). Post-treatment comparisons in these functions with the slow-breathing group were more marked due to improvement in the latter group.

Effects of treatment and breathing exercises on BP and autonomic functions (intragroup comparisons)

No significant change in systolic as well as diastolic BP was recorded in group 1 patients at the end of 3 months of

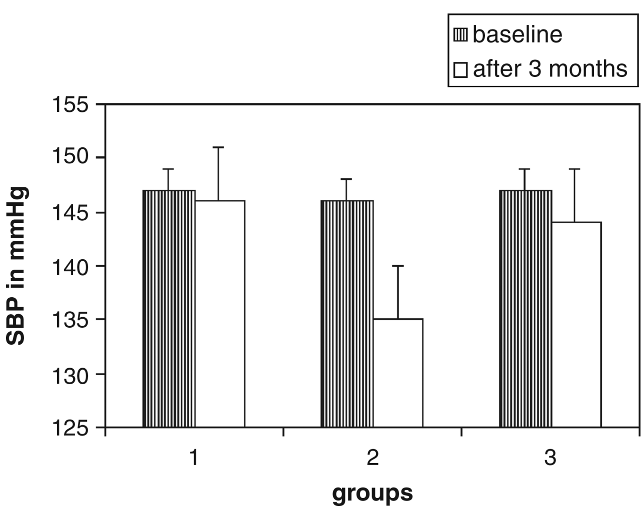

FIG. 1. Comparison of baseline and postintervention systolic blood pressure (SBP) in three groups of hypertensive patients. (Group 1: Patients without intervention; Group 2: Patients prescribed slow-breathing exercises; Group 3: Patients prescribed fast-breathing exercises; $n = 20$ each). All values represent mean with standard deviation.

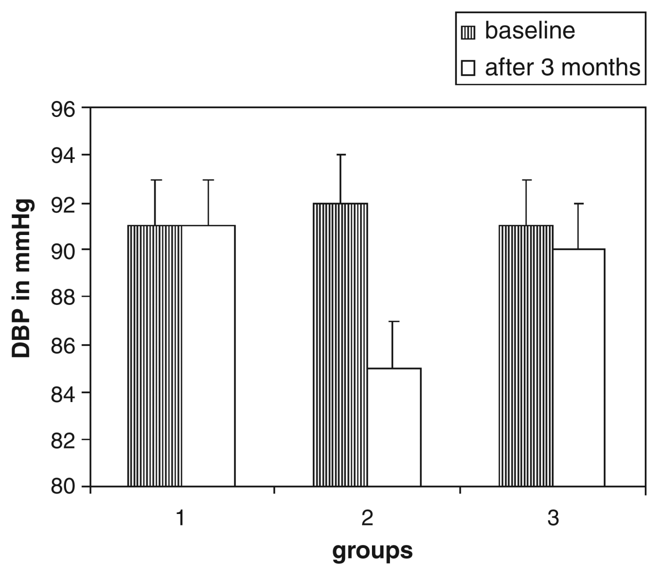

FIG. 2. Comparison of baseline and postintervention diastolic blood pressure (DBP) in three groups of hypertensive patients. (Group 1: Patients without intervention, Group 2: Patients prescribed slow breathing exercises, Group 3: Patients prescribed fast breathing exercises; $n = 20$ each). All values represent mean with standard deviation.

Table 2. Autonomic Function Test of the Three Groups of Patients

Subject no.	*Parameter*		*Group 1* (n = 20)	*Group 2* (n = 20)	*Group 3* (n = 20)
1	S/L ratio	A	0.71 ± 0.20	0.62 ± 0.23^{a}	$1.01 \pm 0.22^{b,c}$
		B	0.79 ± 0.15	1.06 ± 0.12^{d}	$0.92 \pm 0.17^{e,f}$
2	30:15 ratio	A	0.91 ± 0.13	0.93 ± 0.13^{a}	$1.02 \pm 3.46^{b,c}$
		B	0.89 ± 0.15	1.06 ± 3.20^{d}	$1.02 \pm 1.45^{e,f}$
3	*Valsalva* ratio	A	1.34 ± 6.92	1.30 ± 7.32	1.35 ± 8.85
		B	1.34 ± 7.18	$1.41 \pm 5.39^{a,d}$	1.35 ± 9.0^{f}
4	E/I ratio	A	1.12 ± 0.13	1.10 ± 2.37^{a}	1.09 ± 2.07
		B	1.09 ± 2.35	1.15 ± 1.72^{d}	1.10 ± 2.15^{f}
5	Handgrip test	A	11 ± 1.77	$12 \pm 2.60^{a,g}$	11 ± 1.88^{c}
		B	11 ± 1.9	16 ± 1.84^{d}	11 ± 1.75^{f}
6	Cold pressor response				
	Rise in SBP	A	13 ± 2.28	12 ± 2.01^{a}	11 ± 1.65^{b}
		B	13 ± 1.89	16 ± 1.70^{d}	$11 \pm 1.43^{e,f}$
	Rise in DBP	A	8 ± 1.58	8 ± 1.53^{a}	8 ± 1.34
		B	9 ± 1.17	13 ± 1.34^{d}	9 ± 1.00^{f}

All values are mean ± standard deviation. Comparison using paired and unpaired *t*-test; $p < 0.05$ is significant. A represents baseline values and B represents values after 3 months of treatment and breathing exercises.

[a]Significant intragroup comparison (baseline with 3 months of treatment and breathing exercises).
[b]Significant intergroup comparison at baseline, groups 1 & 3.
[c]Significant intergroup comparison at baseline, groups 2 & 3.
[d]Significant intergroup comparison at 3 months, groups 1 & 2.
[e]Significant intergroup comparison at 3 months, groups 1 and 3.
[f]Significant intergroup comparison at 3 months, groups 2 and 3.
[g]Significant intergroup comparision at baseline, groups 1 and 2.

S/L ratio, standing-to-lying ratio; E/I ratio, heart rate variation with respiration; SBP, systolic blood pressure; DBP, diastolic blood pressure.

study compared to their baseline value. However, a highly significant decrease in systolic as well as diastolic BP was recorded in both group 2 ($p = 0.000$, 0.000) and group 3 ($p = 0.004$, 0.003), although the decrease was greater in group 2 (Figs. 1 and 2). A significant increase in S/L ratio, 30:15 ratio, *Valsalva* ratio, E/I ratio, diastolic BP increase in HGT, and both diastolic and systolic BP increase in cold pressor test was observed in group 2 only when compared with baseline values ($p = 0.000$ for each; Table 2).

Within-group analysis using repeated-measures ANOVA showed significant change in systolic and diastolic BP for groups 2 and 3, and autonomic functions in group 2 only ($p = 0.017$, 0.003 for group 3 systolic and diastolic BP, $p = 0.000$ for all others.)

Discussion

Our results clearly demonstrated autonomic dysfunction in patients with hypertension, and a decreased systolic and diastolic BP with breathing exercises and an alteration in autonomic function in patients practicing slow-breathing exercises. The impaired parasympathetic and sympathetic reactivity suggests disturbances in the autonomic nervous system's control on cardiovascular function. The decreased BP in patients receiving breathing exercises suggests their therapeutic role. All patients in group 1 and 60% in groups 2 and 3 were already on antihypertensive therapy. Since improvement in BP was seen in groups 2 and 3 and not in group 1, the beneficial effect can be attributed to breathing exercises.

Slow-breathing exercises prescribed were compatible with those used in yogic practices of savitri pranayama (breathing with end-inspiratory and end-expiratory breath holding in fixed ratios) and nadishoddhna pranayama (alternate-nostril breathing). Many studies using similar yogic practices, breathing devices with or without interactive music that lead to slowing of respiration, have similarly reported improvement in cardiovascular variables such as heart rate, BP, and double product in patients with hypertension.[26–30] Some of these studies have used different breathing protocols for the same patients, whereas others have combined asanas (yogic postures) with breathing exercises. In comparison, our subjects learned a single breathing protocol without any device. The aim was to make it comparable it to a real-life situation, to ensure compliance and long-term acceptability. In addition, we have done both inter- and intragroup comparisons.

It is known that breathing modulates both sympathetic and parasympathetic neural drive to the heart, and autonomic control areas of respiration and cardiovascular areas are, anatomically and functionally, closely located in the brainstem.[31,32] Also during spontaneous ventilation, changes in both tidal volume and rate of ventilation modulate heart rate variability and autonomic function,[29,33] and different breathing patterns and controlled breathing protocols have been used to study this.[34,35] It is believed that yogic breathing exercises such as *surya anuloma viloma pranayama* (right-nostril breathing) improve sympathetic tone or decrease vagal tone.[24,36] In this study by Raghuraj et al., the volunteers were already familiar with the breathing techniques, and acute or short-term effects were measured. All these mechanisms are likely to explain the cardiovascular response associated with different breathing practices and can also explain the improvement in autonomic function in our patients practicing the slow-breathing exercise. However, another study suggests that the increase in high-frequency amplitude, decrease in ratio of low-frequency to high-frequency component of R-R interval, and no change in the mean R-R interval with increasing respiratory interval is respiratory related vagal modulation of the heart rate that does not reflect either an increase in vagal tone or a decrease in sympathovagal balance.[37] One important inference of our study is that slow breathing can improve BP and autonomic functions in patients uncontrolled by drugs. This should be kept in mind by all treating physicians before thinking of increasing the dose, or changing the antihypertensive therapy with all its expense and side-effects. Larger trials in different stages of hypertension are needed to substantiate this.

Fast breathing, however, leads to sympathetic activation. A higher respiratory rate is associated with increased level of sympathetic traffic and potentiation of chemoreceptor response to hypoxia and hypercapnia.[13] Fast breathing or "breath of fire" increases the low-frequency heart rate oscillation and mean resting heart rate, which may result in a so-called "meditation paradox."[38] Bhastrika (forceful inhalation and exhalation) and kapalbhati (deep inhalation with forceful exhalation) are such forms of yogic breathing practices that involve forceful contraction of inspiratory muscles.[39] Although subjects performing bhastika showed an increase in heart rate, no change in both systolic and diastolic BP was reported. Patients with rapid breathing as seen in heart failure show a high degree of sympathetic activation.[40] In our hypertensive patients on a fast-breathing regimen, no significant alteration in autonomic function was observed. Similar results with no change in autonomic function, BP response to cold pressor test have been reported earlier.[9,41] The study of Pal et al. evaluated normotensive individuals. In addition, we have used hand grip and cold pressor tests, which are better indicators of sympathetic reactivity. Perhaps a faster breathing rate would have led to a different response. However, ethical reasons and protocols of fast-breathing yogic exercises were kept in mind while selecting this rate of breathing. It would be interesting to study a larger group and individual variations in future.

This study had a few limitations. It would have been better to record BP over several days for both baseline and postintervention data or to record ambulatory BP. This is advisable and should be done if compliance or loss of ambulatory BP instruments is not an issue as in all admitted patients. Also, patients in the control group had visited the outpatient department once a week and yoga clinic once a month, and had less interaction with the hospital staff compared to other groups. Similarly, the psychologic aspect of doing "some intervention regularly" could have influenced the results. Also, since the patients were already on drugs, randomly chosen, and were not homogeneous in terms of the antihypertensive therapy received and baseline autonomic function, it is not possible to comment on the effect of an individual antihypertensive drug on autonomic functions. This is another lacuna of this study.

Conclusions

In conclusion, this study has shown autonomic dysfunction associated with increase in BP in patients with essential hypertension. Both slow- and fast-breathing exercises improve the BP control. The mechanism involves improvement in autonomic function in those practicing slow breathing, while in this protocol of fast breathing there is no significant change in autonomic functions of patients with hypertension. The improvement in BP is perhaps due to the generalized beneficial effect of exercise. It is therefore suggested that patients with hypertension who desire but are unable to adhere to a complete yogic regimen are likely to benefit by practicing easily learned slow-breathing exercises. Also, not all fast-breathing exercises are necessarily contraindicated in patients with hypertension.

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Disclosure Statement

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