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Slow breathing exercise improves cardiac autonomic tone in hypothyroid patients: a frequency domain analysis of HRV

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Abstract

Background: Hypothyroidism is associated with autonomic dysfunction and oxidative stress. Slow breathing exercise (SBE), a yoga-based relaxation technique, improves cardiac autonomic nerve function by changing sympathetic or parasympathetic activity. **Objective:** To assess the effect of SBEon cardiac autonomic tone and in hypothyroid patients. **Methods:** This non randomized controlled trial was conducted on 50 newly diagnosed drug naive female hypothyroid patients (18-45 years of age)recruited from the outpatient department of the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University,(BSMMU), Shahbag, Dhaka. Twenty five apparently healthy female subjects formed control group. . Among the 50 hypothyroid patients, 25 were consecutively assigned with SBE for 90 days (Group SBE) and the remaining 25 patients were without SBE and followed up after 90 days (Group NSBE). Both groups of patients received treatment with thyroid hormone replacement during their follow up period. Control group did not perform SBE or any other exercise. Data were recorded at baseline(Day 0) and after 90 days in all the subjects. Based on data recording period SBE group was designated as SBE_0(at day 0 or pre intervention)and SBE_{90}(at day 90 or post intervention). Similarly, $NSBE_0$(day 0) and $NSBE_{90}$ (day 90) and control group was also designated as $control_0$ (day 0) and $control_{90}$ (day 90).Resting cardic autonomic tonic activity was assessed by frequency domain analysis of Heart Rate Variability(HRV). HRV data were recorded by a digital data acquisition device Power Lab, AD Instrument Australia. Data were expressed as mean±SD. For statistical analysis, ANOVA followed by post hoc Bonferroni test and paired sample "t" test were done. **Results:** At baseline i.e. at day 0 before follow up, diastolic blood pressure (DBP) ($p<0.05$), low frequency in normalized unit (LF norm) ($p<0.001$), low frequency/high frequency ratio (LF/HF) ($p<0.001$) were significantly higher and total power (TP) ($p<0.001$), low frequency power (LF power) ($p<0.01$), high frequency power (HF power) ($p<0.001$), high frequency power in normalized unit (HF norm) ($p<0.001$) were significantly lower in hypothyroid patients (group $SBE_0$and $NSBE_0$) compared to healthy control (group $control_0$). After 90 days of intervention with SBE, SBP, DBP, LF norm, LF/HF ratio decreased significantly and TP, HF power, HF norm increased significantly in group SBE_{90} compared to SBE_0. Whereas, in group $NSBE_{90}$, after 90 days of follow up, LF norm, LF/HF ratio decreased significantly and HF power, HF norm increased significantly compared to $NSBE_0$. Again, after 90 days of follow up/SBE, HF norm were significantly higher and LF norm, LF/HF ratio were significantly lower in SBE_{90} compared to $NSBE_{90}$. In addition, significant difference was present in all these parameters between $NSBE_{90}$ and $control_{90}$. Also, after 90 days of SBE, LF norm, HF norm and LF/HF ratio was not significantly different from control. **Conclusions:** Based on these results, it can be concluded that autonomic dysfunction characterized by reduced vagal tone and sympathetic hyperactivity occurred in drug naïve hypothyroid patients. In addition, thyroid hormone replacement therapy improved autonomic dysfunction by increasing parasympathetic and decreasing sympathetic tonic activity. Moreover, SBE caused further improvement of autonomic dysfunction and could restore sympathovagal balance to its normal state in these patients.

Key words: Heart rate variability, hypothyroid, slow breathing exercise.

Introduction

Hypothyroidism is a common global endocrine disorder. Its prevalence is 4-5% in the developed countries, whereas greater prevalence 7-10% has been noted in developing countries including India and Bangladesh.[1-2] Thyroid hormone deficiency is associated with various cardiovascular abnormalities like impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance and cardiac electrical abnormalities. If it remains undiagnosed or improperly treated, hypothyroidism causes changes in autonomic regulation of cardiovascular system[3].The autonomic nervous system, through its dual pathways, influences every organ in the body including cardiovascular system.

Sympathetic nerve accelerates whereas parasympathetic nerve slows the heart rate. At rest, both sympathetic and parasympathetic nerves are tonically active with dominant vagal effects. Therefore, resting heart rate reflects the balance between sympathetic and parasympathetic systems. The clinical features of hypothyroidism including bradycardia, decreased cardiac contractility, narrow pulse pressure and low level of thermo-genesis suggests sympathetic hypoactivity in these patients. But in contrary to the clinical picture, hypothyroidism is associated with sympatho-vagal imbalance with relatively increased sympathetic activity and reduced vagal activity[3-8]. In hypothyroidism, increased thyrotropin releasing hormone (TRH) directly stimulates sympathetic outflow resulting in increased norepinephrine release from sympathetic nerves. But the clinical features suggesting hypoactive sympathetic function might be linked to desensitization at receptor and/or post receptor level.[3-4, 6, 9-10] Due to this sympathetic and parasympathetic influence, heart rate is irregular which is apparent when heart rate is examined on a beat-to-beat basis.[11]

Heart rate variability (HRV) is a sensitive, very accurate, non-invasive digitized tool for assessing the resting activities of cardiac autonomic nerves. It measures beat-to-beat change in heart rate as well as discharge of resting tonic of both sympathetic and parasympathetic nerves and their balance.[12-15] Reduced HRV acts as a strong predictor of risk for adverse events in patients with broad range of diseases and mortality.[11,16]

Recent investigation on yoga based relaxation technique has demonstrated improvement in autonomic function, cardiovascular & respiratory function in both health and diseases.[17-20]. Slow breathing exercise is a yoga based relaxation technique and its Regular performance improves autonomic functions by decreasing tonic sympathetic activity or by increasing vagal tone.[17] The good impact of SBE on cardiac autonomic tone in various diseases has been published but little is known about its effect on dysautonomia in hypothyroids. Therefore, this study was designed to assess the effect of slow breathing exercise on cardiac autonomic nerve function in female hypothyroid patients.

Methods

Design setting and study participants

This non randomized controlled trial was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University(BSMMU), Shahbag, Dhaka from March 2021 to February 2022. Fifty (50) newly diagnosed female hypothyroid patients(18-45 years of age were selected by purposive sampling from outpatient department of the Department of Endocrinology, BSMMU, Shahbag, Dhaka, and 25 apparently healthy female subjects formed control group. Twenty five patients were assigned with SBE and form SBE group and 25 patients were not under SBE and they formed NSBE group.

Selection criteria

Pregnant or lactating women, postmenopausal women, patients with cardiovascular disorders, neurological disorders, respiratory disorders, diabetes mellitus, renal insufficiency, hyperthyroidism, arthritis, liver diseases, irritable bowel syndrome, neoplastic disease, autoimmune diseases other than Hashimoto's thyroiditis, already performing yoga or breathing exercise, under medications for cardiac disease or respiratory disease or for other reasons which may interfere with autonomic nervous system balance were excluded.

Intervention with SBE

SBE protocol was explained meticulously and active demonstration was given to the patients of the 'study group' designated for SBE & trained to perform steps of SBE till they were confident to perform it independently at home. They were advised to perform SBE every morning & evening for 30 minutes for a period of 90 days duration and to continue with the conventional treatment. In order to ensure compliance an exercise diary was provided to each subject where date, duration and steps of SBE was written and they were trained on how to record information after completion of each session. The subjects were regularly monitored by frequent home visits and encouraged to be the part of this study by maintaining regular communication through telephonic calls several times a week. The patients were followed up at the Department of Physiology, BSMMU when needed. Group NSBE continued only conventional treatment. Both study groups SBE and NSBE were requested to report to the Department of Physiology, BSMMU, after 90 days to record all the study variables.

Control group did not practice SBE. On the basis of data recording time SBE group was designated as SBE_0 (at day 0 or pre intervention) and SBE_{90} (at day 90 or post intervention). Similarly, group NSBE was also designated as $NSBE_0$ (day 0) and $NSBE_{90}$ (day 90) and control group was also designated as group $control_0$ (day 0) and $control_{90}$ (day 90).

Data collection procedure

After explaining the objective and detail procedure of the study an informed written consent was collected from all participants. Then a detailed personal, familial, menstrual and medical history was taken and a thorough clinical examinations were done and documented in a pre fixed data sheet. In the previous night of test day, all subjects were advised to finish meal before 9:00AM and to have a restful sleep, not to take any sedative or any drug affecting CNS. On the test day, the subjects were requested to report with a light breakfast without tea or coffee, to the lab for HRV data recording. Before recording subjects were allowed to take complete bed rest in supine position for 30 minutes in a cool and calm environment of Noorzahan Begum Neurophysiology Research lab in the Department of Physiology but to refrain from talking, drinking, eating and stay calm and quiet but not to sleep. The recording of HRV measures was done by 8 active channels, Power Lab 8/35 (AD instrument, Australia). The frequency domain measures, such as total power(TP),HF, HFnu, LF, LFnu and LF/HF were auto generated by software by analyzing the RR interval from the ECG recorded for 5 minutes.

Statistical analysis

Data were expressed as mean±SD. Statistical analysis was performed by using SPSS for Windows, Version 16. Data were analyzed by Shapiro Wilk test. One Way Variance (ANOVA) followed by post hoc Bonferroni test and also paired sample t test. P value < 0.05 was considered as statistical significance.

Results

In this study, both the patient groups and control group were comparable for age and BMI (Table I).

Table I : Age and BMI in different groups (N=75)

Variables	SBE (n=25)	NSBE (n=25)	Control (n=25)
Age (Years)	35.16±6.87	31.68±7.44	31.28±4.34
	(22-45)	(19-45)	(21-39)
BMI (Kg/m^2)	26.88±4.53	25.34±3.89	24.24±3.65
	(19.48-37.28)	(18.36 - 33.33)	(18.49-33.25)

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by One-way ANOVA; BMI- Body Mass Index; SBE- Patients with slow breathing exercise; NSBE- Patients without slow breathing exercise; Control- Healthy control; N- Total number of subjects; n- Number of subjects in each group.

Among the frequency domain parameters of HRV, the mean total power (TP), LF power, HF power and HF norm were significantly lower and mean of LF norm and LF/HF ratio were significantly higher in group SBE_0 ($p<0.001$, $p<0.01$, $p<0.001$ and $p<0.001$) and $NSBE_0$ ($p<0.001$, $p<0.01$, $p<0.001$ and $p<0.001$) than that of $Control_0$. No statistically significant difference was observed in these parameters when compared between SBE_0 and $NSBE_0$(Table II).

Table II : Frequency domain measures of HRV in different groups at baseline (N=75)

Variables	SBE_0(n=25)	$NSBE_0$(n=25)	$Control_0$(n=25)
TP(ms²)	970.91±1101.99***	833.08±741.80***	2982.68±1897.88
	(176.70-4617.00)	(183.60-3229.00)	(1296.00-9265.00)
LF power(ms²)	280.05±283.24**	258.76±313.63**	679.47±660.03
	(43.34-1210.00)	(32.30-1400.00)	(152.70-3232.00)
HF power(ms²)	170.68±131.15***	167.33±171.38***	1506.38±1022.94
	(18.85-566.80)	(25.91-628.90)	(526.70-4615.00)
LF norm(nu)	58.06±14.55***	58.61±19.15***	30.28±11.29
	(33.48-87.83)	(23.21-86.04)	(8.00-49.78)
HF norm(nu)	40.38±14.86***	41.02±18.02***	67.92±11.64
	(13.52-65.73)	(14.93-75.68)	(44.98-90.50)
LF/HF ratio	1.88±1.45***	1.94±1.40***	0.49±0.25
	(0.51-6.50)	(0.31-5.70)	(0.09-1.11)

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by One-way ANOVA followed by post-hoc Bonferroni test. TP- Total power; LF power- Low frequency power; HF power- High frequency power; LF norm- Low frequency power in normalized unit; HF norm- High frequency power in normalized unit; LH/HF ratio- Low frequency power/High frequency power ratio; SBE_0- Patients with slow breathing exercise at baseline; $NSBE_0$- Patients without slow breathing exercise at baseline; $Control_0$- Healthy control at baseline; N- Total number of subjects; n- Number of subjects in each group. *This depicts comparison with control group, $^{**}p<0.01$, $^{***}p<0.001$.

After 90 days of intervention with SBE the mean TP, HF power and HF norm significantly increased ($p<0.001$, $p<0.01$ $p<0.001$) and LF norm and LF/HF ratio significantly decreased ($p<0.001$) in SBE_{90} compared to SBE_0. Similarly, HF power and HF norm significantly increased ($p<0.05$) and LF norm and LF/HF ratio significantly decreased ($p<0.01$) in $NSBE_{90}$ after 90 days of follow up compared to $NSBE_0$. (Table III).

After 90 days of observation the mean HF norm was found significantly higher ($p<0.001$) but LF norm and LF/HF ratio were significantly lower ($p<0.001$) in SBE_{90} compared to $NSBE_{90}$ but were comparable with $Control_{90}$. In addition, the mean TP, LF power and HF power were observed significantly lower ($p<0.01$, $p<0.05$ and $p<0.01$) in SBE_{90} group than that of $Control_{90}$ group. In $NSBE_{90}$ group, TP, LF power, HF power and HF norm were found significantly lower ($p<0.001$, $p<0.01$, $p<0.001$ and $p<0.001$) and LF norm and LF/HF ratio were found significantly higher ($p<0.001$) than that of $Control_{90}$ group (Table IV).

Table III : *Pre and post intervention/follow up values of frequency domain measures of HRV in hypothyroid patients (N=50)*

Variables	SBE_0(n=25)	SBE_{90}(n=25)	$NSBE_0$(n=25)	$NSBE_{90}$(n=25)
TP(ms²)	970.91±1101.99	1809.39±1428.01¥¥¥	833.08±741.80	936.67±696.72
	(176.70-4617.00)	(524.90-6088.00)	(183.60-3229.00)	(396.80-2976.00)
LF power(ms²)	280.05±283.24	411.02±446.10	258.76±313.63	285.85±334.12
	(43.34-1210.00)	(51.08-1941.00)	(32.30-1400.00)	(52.49-1420.00)
HF power(ms²)	170.68±131.15	810.64±903.52¥¥	167.33±171.38	256.57±212.41§
	(18.85-566.80)	81.62-4093.00)	(25.91-628.90)	(43.32-1039.00)
LF norm(nu)	58.06±14.55	33.97±12.59¥¥¥	58.61±19.15	48.88±12.67§§
	(33.48-87.83)	(18.40-64.70)	(23.21-86.04)	(24.61-68.28)
HF norm(nu)	40.38±14.86	63.81±11.97¥¥¥	41.02±18.02	49.02±12.13§
	(13.52-65.73)	(33.26-78.29)	(14.93-75.68)	(29.29-73.59)
LF/HF ratio	1.88±1.45	0.60±0.41¥¥¥	1.94±1.40	1.12±0.56§§
	(0.51-6.50)	(0.25-1.95)	(0.31-5.70)	(0.35-2.33)

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by Paired sample t-test; TP- Total power; LF power- Low frequency power; HF power- High frequency power; LF norm- Low frequency power in normalized unit; HF norm- High frequency power in normalized unit; LH/HF ratio- Low frequency power/High frequency power ratio; SBE_0- Patients with slow breathing exercise at baseline; SBE_{90}- Patients with slow breathing exercise at the end of 90 days; $NSBE_0$- Patients without slow breathing exercise at baseline; $NSBE_{90}$- Patients without slow breathing exercise at the end of 90 days; N-Total number of subjects; n- Number of subjects in each group. ¥This depicts comparison between SBE_0 and SBE_{90} group,¥¥$p<0.01$ ¥¥¥$p<0.001$. §This depicts comparison between $NSBE_0$ and $NSBE_{90}$ group, §$p<0.05$, §§$p<0.01$.

Table IV : Post intervention/follow up values of frequency domain measures of HRV in different groups (N=75)

Variables	SBE_{90}(n=25)	$NSBE_{90}$(n=25)	$Control_{90}$(n=25)
TP(ms²)	1809.39±1428.01$^{##}$	936.67±696.72$^{###}$	3451.26±2689.89
	(524.90-6088.00)	(396.80-2976.00)	(49.55-9860.00)
LF power(ms²)	411.02±446.10$^{#}$	285.85±334.12$^{##}$	763.74±621.23
	(51.08-1941.00)	(52.49-1420.00)	(184.10-2200.00)
HF power(ms²)	810.64±903.52$^{##}$	256.57±212.41$^{###}$	1901.59±1723.81
	81.62-4093.00)	(43.32-1039.00)	(416.30-6807.00)
LF norm(nu)	33.97±12.59$^{$$$}$	48.88±12.67$^{###}$	29.25±11.14
	(18.40-64.70)	(24.61-68.28)	(12.71-50.23)
HF norm(nu)	63.81±11.97$^{$$$}$	49.02±12.13$^{###}$	68.62±10.88
	(33.26-78.29)	(29.29-73.59)	(48.62-81.98)
LF/HF ratio	0.60±0.41$^{$$$}$	1.12±0.56$^{###}$	0.47±0.27
	(0.25-1.95)	(0.35-2.33)	(0.16-1.03)

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by One-way ANOVA followed by post-hoc Bonferroni test. TP- Total power; LF power- Low frequency power; HF power- High frequencyz power; LF norm- Low frequency power in normalized unit; HF norm- High frequency power in normalized unit; LH/HF ratio- Low frequency power/High frequency power ratio; SBE_{90}- Patients with slow breathing exercise at the end of 90 days; $NSBE_{90}$- Patients without slow breathing exercise at the end of 90 days; $Control_{90}$- Healthy control at the end of 90 days; N- Total number of subjects; n- Number of subjects in each group. $^{#}$This depicts comparison with $control_{90}$ group, $^{#}p<0.05$, $^{##}p<0.01$, $^{###}p<0.001$. $^{\$}$This depicts comparison of SBE_{90} with $NSBE_{90}$ group, $^{\$\$\$}p<0.001$.

Discussion

This study observed the effect of SBE on CANF in female hypothyroid patients by analysis of frequency domain of HRV. In this study, two vital confounding variables, age and BMI, were adjusted in all 3 groups making them comparable.

In this study, lower TP, LF power, HF power and HF norm in both groups of patients prior to SBE/ follow up suggested that impaired vagal tone was associated with hypothyroid patients which was consistent with reports of previous studies.[3-4,6-8,21-24]

On the other hand, higher LF norm and LF/HF ratio in hypothyroid patients prior to intervention/follow up suggested sympathetic hyperactivity and sympathetic dominated autonomic imbalance in these hypothyroid patients which also agree to previous studies.[3-4,6-8,21-22,24]

The autonomic dysfunction in the current series of hypothyroid patients occurred due to direct stimulating effect of TRH on autonomic neuron in thoracolumbar segment of spinal cord resulting in increased norepinephrine release from sympathetic nerve ending.[9] This autonomic imbalance may limit the dynamic flexibility of the heart to cope up the environmental challenge and it poses threat to cardiovascular health.

After 90 days of intervention with SBE along with hormone replacement therapy, significant increment of TP, HF power and HF norm and significant decrement of LF norm and LF/HF ratio suggested improvement of impaired autonomic balance as well as improvement of sympathetic and parasympathetic dysfunction in hypothyroid patients.

Again, after 90 days of follow up without SBE and only under hormone replacement therapy, significant increment of HF power and HF norm and significant decrement of LF norm and LF/HF ratio suggested also improvement of impaired autonomic balance as well as improvement of sympathetic and parasympathetic dysfunction in hypothyroid patients.

But, significantly higher value of HF norm and lower values of LF norm and LF/HF ratio in patients under SBE compared to patients without SBE after 90 days of intervention/follow up proved that SBE effectively improved sympathetic and parasympathetic dysfunction thereby corrected the autonomic imbalance and thyroid hormone therapy may be attributed into this effect.

Moreover, SBE restored HF norm, LF norm, LF/HF ratio in hypothyroid patients to control level. These findings reflected the additional effect of SBE therapy over medication on the improvement of CANF in hypothyroid patients.

Some other researchers found similar effect of SBE frequency domain parameters of HRV in migraine, type-2 diabetes mellitus and transfusion dependent thalassemic patients.[25-27]

In this study, improvement of HRV in hypothyroid patients was evident after both hormone replacement therapy and SBE. SBE could restore some of the parameters to control level whereas, only hormone replacement therapy could not. Hypothyroid patients who performed SBE in addition to hormone replacement therapy showed greater improvement in CANF compared to patients who did not.

But the neural mechanism responsible for this autonomic shift is largely unknown. It is clearly evident that respiration and parasympathetic response are intricately connected but, the cellular mechanism that integrates respiration and parasympathetic response is not clear yet. The improvement in CANF in this present series of hypothyroid patients was possibly due to the following fact. During inhalation and retention of SBE, excess expansion of lung above tidal volume activates two types of receptors- slowly adapting stretch receptors (SAR) of the lungs and stretch of connecting tissue fibroblasts surrounding lungs producing inhibitory neural impulse and hyperpolarization current. Inhibitory impulse synchronizes rhythmic cellular activity between the cardiopulmonary center and the central nervous system. The inhibitory synchronized activity elicits parasympathetic dominance. In addition, hyperpolarization current modulate neuronal excitability, resting membrane potential, generate rhythmic brain activity and inhibits unsynchronized neuronal input thereby increasing the dominance of synchronized input. Thus stretch-induced inhibitory signals and hyperpolarization currents within neural and non-neural tissue synchronizes neural elements in the central nervous system, peripheral nervous system, and surrounding tissues and ultimately resets the autonomic nervous system and shifts in the autonomic balance towards para-sympathetic dominance.[28]

Conclusion

From the results of this study, it can be concluded that autonomic dysfunction characterized by reduced vagal tone and sympathetic hyperactivity with sympathetic dominant autonomic imbalance may occur in hypothyroid patients. Regular performance of slow breathing exercise for a substantial period was effective to increase parasympathetic activity, decrease sympathetic activity and restore sympathovagal balance to its normal state in hypothyroid patients.

Thyroid hormone replacement therapy was also effective to correct autonomic dysfunction in drug naïve hypothyroid patients. In addition, SBE may provide additional improvement of autonomic dysfunction to the thyroid hormone therapy induced correction of autonomic dysfunction in hypothyroid patients.

So, SBE is an effective measure to improve autonomic dysfunction in addition to hormone therapy and can be successfully used as an adjunct to thyroid hormone replacement therapy and thereby protect the hypothyroid patients from cardiovascular risk. Therefore, SBE can be recommended for hypothyroid patients as a part of complementary medicine to protect these patients from cardiovascular morbidity.

Conflict of interest None

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