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IMPACT OF NON-INVASIVE VAGUS NERVE STIMULATION ON SELECTED CARDIAC PARAMETERS IN CHRONIC HEART FAILURE

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Abstract

Background: Chronic heart failure is a crucial health threat that has a significant negative impact on sufferers' quality of life. Transcutaneous electrical stimulation of cervical vagus nerve is a non-invasive approach, and it might be useful for a large population of HF patient.

Objective: To evaluate the efficacy and safety of non-invasive vagus nerve stimulation as an adjuvant treatment of chronic heart failure.

Methods: Forty patients with chronic heart failure (NYHA- functional class II-III) with ejection fraction ≤40% participated in this study. Subjects were divided into 2 groups: Group A received tVNS, and Group B received sham tVNS; their ages ranged from 50 to 65 years old. Functional capacity level using the six-minute walk test, health-related quality of life via Minnesota Living with Heart Failure Questionnaire (MLHFQ), and heart muscle function via non-invasive echocardiogram (echo) to assess ejection fraction (EF), end-systolic volume (ESV), and end-diastolic volume (EDV), were measured pretreatment, after one session and posttreatment.

Results: No significant difference between groups pre-treatment ($p > 0.05$). There was significance increase in 6MWT, and obvious improvement in MLHFQ, plus remarkable increase in heart function 'EF, and decrease in ESV and EDV' of group A compared with that of group B post treatment ($p < 0.05$).

Conclusion: Adding tVNS to conventional treatment is a safe and effective method that may enhance function capabilities, health-related quality of life, and heart muscle function in patients with chronic heart failure.

Keywords: Non-invasive vagus nerve stimulation, chronic heart failure, Ejection fraction, 6-minute walk test, Minnesota Living with Heart Failure Questionnaire

INTRODUCTION

Chronic heart failure (CHF) is a serious worldwide health disorder with obvious burden worldwide, also CHF has consequently negative socioeconomic, financial impacts those accounts for considerable healthcare and socioeconomic costs and degraded quality of life [1]. Currently, estimated worldwide prevalence of CHF is nearby 38 million worldwide, and still increasing with aging. Individuals with CHF often have features of autonomic dysfunction characterized by excessive sympathetic activation and concomitant parasympathetic withdrawal [2].

Evidence indicates that patients with CHF have features of autonomic dysfunction characterized by excessive sympathetic activation and concomitant parasympathetic withdrawal [2]. Almost Clinicians specify New York Heart Association (NYHA) classification at baseline after the initial diagnosis and after treatment through the continuum of care. CHF is typically a long-term condition that gradually worsens over time [3].

Therefore, numerous clinical tests utilized to evaluate the function of cardiac muscle. Echocardiogram: an ultrasound of the heart routinely used to identify cardiac abnormalities [4].

Numerous alternative therapeutic approaches have been focused on control symptoms and improve functional capacity, reduce hospitalizations and decrease mortality [5]. Despite the widespread use of pharmacologic therapy and devices, the overall prognosis of HF patients remains poor and new therapies are needed [6]. While much of the emphasis in treating HF has over the past decade or two focused on modulation of sympathetic activity, considerable interest has emerged recently in modulating parasympathetic or vagal activity as a therapeutic target for treating CHF [7].

Vagus nerve stimulation (VNS) has been used clinically for twenty-five years, it is an FDA-approved therapy tool andits safety profile has been well established [8].

In addition, there is still limited understanding on the physiology of the vagus nerve in humans, as well multi- organ responses in response to vagus nerve stimulation (VNS), despite over 130,000 VNS implants worldwide to treat epilepsy, depression, anxiety, gastrointestinaldisorders, rheumatoid arthritis, and stroke recovery. The majority of visceral organs receive dual innervation from the sympathetic and parasympathetic divisions of the autonomic nervous system, and these play many important roles in the homeostatic adjustments in organ function essential for life [9].

Although systematic reviews have shown that tVNS is safe and well tolerated. A great deal of supplementary evidence is required, including controversial issues of unilateral or bilateral and left or right stimulation [10]. Therefore, current study was conducted to evaluate the efficacy and safety of non-invasive vague nerve stimulation as an adjuvant treatment of chronic heart failure.

Subject, Material &Methods

This study was designed as a Prospective, Pre/ Posttreatment, randomized controlled trial. After approval of the ethical committee of the Faculty of Physical Therapy, Cairo University- Egypt (P.T.REC/012_002333), the procedures of the present study were discussed thoroughly and all the participants were asked to sign a written informed consent. Upon the results of the pilot study and by using G*POWER statistical software (version 3.1.9.2; Franz Faul, University at Kiel, Germany). The sample size was calculated as a function of the expected change in using means and standard deviations extracted from a previous study effect of vagal nerve stimulation according to De Ferrari et al [11]. thus current study power has been set to 0.80, and two-tailed analysis with equal groups and p-value

0.05 has been performed, number of main outcome measures was forty , for two groups, thus the suggested was 20 patients in each group under the assumption of a two- sided type I error of 5% and a power of 80%, effect size of 0.458.

Participants

Forty male and female participants allocated randomly into two groups (twenty patient per group), their age ranged from 50 to 65 years old, were selected randomly from Sohag University Hospital, during the period of March 2022 to March 2023.

Group A: had received active transcutaneous vagus nerve stimulation (tVNS) was performed one session per week for eight weeks.

Group B: had sham tVNS, only, one session per week for eight weeks. Randomization were conducted using a computer-generated randomized table using SPSS program “version 23 for windows; SPSS Inc., Chicago, Illinois, USA”. Each participant had one identification number that was used to assign participants into two equal groups in number (n 20),

sequentially numbered index cards were secured in opaque envelopes. A researcher opened the sealed envelope and allocated the participants according to their groups.

Inclusion Criteria

Participants` age ranged from 50 to 65 years old, they had assured diagnosis of chronic heart failure (NYHA- functional class II-III). All participants had LVEF ≤40%, also participants have to be in sinus rhythm, clinically stable for at least 3 months with no change in treatment 'with optimized medical therapy' for at least one month.

Exclusion Criteria

All participants with acute coronary syndrome, coronary revascularization, previous stroke, neck surgeries, sever renal or hepatic, individuals have active peptic disease or history of upper gastrointestinal bleeding, or cardiac surgeries in proceeding six months, insulin-dependent diabetic patients or with diabetic neuropathy, as well whom have secondary or third-degree atrioventricular block; atrial fibrillation or flutter in the previous three months, or with left bundle branch block and/ or with an indication for cardiac resynchronization, and severe chronic obstructive pulmonary diseases, as well whom their bradycardia limit causing interruption of VNS was set at 55 beats/ minute were excluded from this study.

Instruments Assessment tools

- **Six-minute walk test (6MWT)**

The 6MWT distance is a supervised assessment outcome measure regarding functional capacity in CHF individuals. It has been shown to be simple concept, safe, valid, low cost, reliable and ease to standardization, also accepted for follow-up the effectiveness of therapeutic interventions [12].

- **Minnesota Living with Heart Failure Questionnaire(MLHFQ)**

It is one of the most widely used health-related quality of life questionnaires for CHF population, as it has been shown to be valid and reliable [13].

- **Echocardiogram (Echo)**

It is a non-invasive ultrasound test that to assess the heart's function and structures. Echo is a graphic outline of your heart's movement, where ultrasound (high-frequency sound waves) from a hand-held wand placed on chest to take pictures of heart's valves and chambers [14].

Therapeutic Instrument

- **Chattanooga electric stimulation**

An FDA-approved intellect Portable, mobile transcutaneous electrical nerve stimulation (TENS) unit, attached to silicon electrode Parasym device, Parasym Health, Inc., London, UK, with lead placement on the right and left cervical vagus nerve. It is extraordinary versatility based on simplicity of operation with a logical control system and a large, easy to read graphical LCD.

- **Evaluating Procedures**
- **History taking**

Detailed medical and physical histories was taken from each participant in current clinical trials` groups before starting the study and was recorded in a data recording.

- **Specific outcome measures**
- **6MWT**

Assessed all participants` physical capacity, which were conducted by asking each

participant to walk the maximum distance he has walked during a period time of 6 minutes. This was been done in a marked corridor of 30-metre stretchof unimpeded walkway marked by two cones at both ends of the corridor then calculated the distance covered, while wearing a comfortable clothe [12].

- **MLHFQ**

Minnesota Living with Heart Failure Questionnaire (MLHFQ) is one of the most widely used health-related quality of life questionnaires for patients with heart failure (HF). It provides scores for multidimensions, Physical, socio-economic and emotional/psychological aspects, in 21 items. It is a valid and reliable tool that measuring quality oflife among HF population [13].

- **Echo**

Echocardiography was conducted after tVNS session to assess ejection fraction (EF), end-systolic volume (ESV), and end-diastolic volume (EDV), using the same speckle- tracking algorithm. All echocardiographic measurements were obtained offline and the investigators performing the off-line analysis were blinded to treatment assignment [14].

- **Therapeutic procedures**
- **tVNS *(Group A only)***

Proper counselling the participant about the procedures, then patient have close monitoring patients` symptoms with great attention such as fever, headache, dizziness orweakness, pain swelling, redness, itching, blood in cough or vomiting, difficulty in breathing, then adjust treatment parameters of the TENS device 25Hz, 10-50mA and was adjusted to level of participant sensory threshold, with pulse width at 250ms. Then each participant in group A was positioned supine/ or supported sitting according to participant choice. Then, gel was applied at the two electrodes patches to the neck just “right and left’ at the cervical branch of vagus nerve just above the carotid sheath adjacent to the external jugular vein. tVNS targets cutaneous receptive field of cervical vagal stimulation does not create adverse effects, but it does induce modulating effects on heart rate, blood pressure, or peripheral microcirculation during stimulation procedure. The tVNS stimulation for 20 minutes and was interrupted when heart rate drops below 55$_{bpm}$ [15].

- **Sham tVNS (Group B only)**

The tVNS was performed by placing electrodes and increasing amplitude until participant reported feeling sensation. Participants had been told that the amplitude was reduced slightly to prevent discomfort, but the electrode leads then were disconnected from TENS machine without the participants’ knowledge [15].

- **Safety end-points of the treatment protocol**

Since the primary goal of current study are safety and feasibility, The primary end-point was incidence of any adverse events (System or procedure related) during treatment protocol, Time to first occurrence of unplanned heart failure hospitalization. The tVNS is interrupted when heart rate drops below 55 bpm.

Statistical Analysis

SPSS version 25 was used to conduct the analysis of the current study. The descriptive statistics was done calculatingthe mean, standard deviation (SD) per each group. Inferential statistical analysis was used in the form of paired T- test (test of difference) to compare the pre and post-test measures for each group and to compare between the two groups. The association between outcome measures were analyzed using the Spearman correlation

coefficient. All statistically significant differences had been determined with a confidence interval of 95% and thus level of significance was settled at 0.05 level [16].

RESULTS

Patients' Demographic Data

No statistically significant differences between groupsregarding age, weight height and BMI as t values were - 1.33, 0.11, 0.41 and 0.97 and P values were 0.19, 0.91, 0.67 and 0.97, respectively, table (1).

Table 1: Physical characteristics of patients

	Group A X ± SD	Group B X ± SD	MD	t-value	p-value	Sig.
Age (years)	57.6 ± 3.36	59.8 ± 4.32	-1.45	-1.33	0.19	NS
Weight (kg)	74.12 ± 6.65	75.27 ± 4.98	0.5	0.11	0.91	NS
Height (cm)	165.43 ± 3.48	166.47 ± 3.43	0.8	0.41	0.67	NS
BMI (kg/cm^2)	27.08 ± 2.38	27.15 ± 1.50	-0.05	-0.03	0.97	NS

Effect of treatment on 6MWT, MLHFQ and Echo selected parameters

There was a significant interaction effect of treatment and time (P 0.001). There was a significant main effect time (P 0.001). There was a significant main effect of treatment (P 0.001), (Table 2).

Table 2: Mixed MANOVA for the effect of treatment on 6MWT,MLHFQ and Echo selected parameters

Mixed Manova		
Interaction effect (treatment * time)		
F 6.67	*P 0.001*	*S*
Effect of time		
F 117.63	*P 0.001*	*S*
Effect of treatment		
F 0.786	*P 0.001*	*S*

F value: Mixed MANOVA F value p value: Probability value
S: Significant

Effect of treatment on 6MWTWithin group comparison

A significant increase in 6MWT of group A posttreatment compared with both pre-treatment, after 1st session, and post treatment (P 0.001), where non-significant differ in group B with both pre-treatment, after 1st session, and post treatment (P 0.461).

Between groups` comparison

No significant difference in 6MWT between group A and B pretreatment (p 0.69). However, there was a significant increase in the 6MWT of group A compared with that of group B after 1st session (p 0.02), as well a significant increase in the 6MWT of group A compared with that of group B post treatment (p 0.001), table (3).

Table 3: Mean 6MWT pre, after 1st session, and posttreatment ofboth groups A & B

6 MWT (m)	Pre	1st session	Post	P-value	Sig
	$\overline{X}$ ±SD	$\overline{X}$ ±SD	$\overline{X}$ ±SD		
Group A	252 ± 43.5	285.5 ± 32.5	370.5 ± 40.5	0.01	S
Group B	246.25 ±48.5	253.25 ± 12.5	242 ± 45.5	0.461	NS
MD	5.75	32.25	128.5		
P-value	0.69	0.02	0.001		
Sig	NS	S	S		

X: Mean, SD: Standard deviation, MD:

Effect of treatment on MLHFQWithin group comparison

There was a significant improvement in MLHFQ of group A post treatment compared with pretreatment (p 0.001), while no significant difference in MLHFQ of group B post treatment compared with pretreatment (p 0.036).

Between groups` comparison

No difference in MLHFQ between group A and B pretreatment (p 0.51). There was a significant improvement in MLHFQ of group A compared with that of group B after 1st session and post treatment (p 0.01), table (4).

Table 4: Mean MLHFQ pre, after 1st session, and posttreatment of both groups A & B

MLHFQ	Pre treatment	After 1st session	Post treatment	P-value	Sig
	$\overline{X}$ ±SD	$\overline{X}$ ±SD	$\overline{X}$ ±SD		
Group A	64 ± 7	63 ± 5	23 ± 5	0.001	S
Group B	61 ± 6	60 ± 4	54 ± 6	0.036	NS
MD	3	3	-31		
P-value	0.51	0.51	0.01		
Sig	NS	NS	S		

Effect of treatment on EchoWithin group comparison There was a significant improvement in heart muscle function of group A post treatment compared with pretreatment (p 0.001), as well there was a significant increase in heart muscle function (EF) and decreased (EDV &ESV) of group A post treatment compared with pretreatment (p 0.001).

Between groups` comparison

No significant difference in heart muscle function between group A and B pretreatment (p 0.32). There was a significant improve/ increase in the heart muscle function(EF) of group A compared with that of group B posttreatment (p 0.03, 0.007 and 0.03). as well there was a significant decrease of EDV &ESV of group A compared with that of group B post treatment (p >0.005), table (5).

Table 5: Mean heart muscle function pre, after 1st session, and post treatment of group A and B

Heart muscle function		Pre treatment $\bar{X}$±SD	After 1st session $\bar{X}$±SD	Post treatment $\bar{X}$±SD	P-value	Sig
Ejection fraction	Group A	38 (35-40)	42 (37-43)	44 (38-46)	0.001	S
	Group B	37 (35-41)	37 (36-41)	37 (36-41)	0.34	NS
	P-value	0.32	0.03	0.006		
	Sig	NS	S	S		
End-systolic volume	Group A	148 ± 30.5	135 ± 25.5	130 ± 20.5	0.003	S
	Group B	151 ± 35.5	151 ± 32.5	150 ± 25.5	0.63	NS
	MD	-3	-16	-20		
	P-value	0.32	0.007	0.004		
	Sig	NS	S	S		
End-diastolic volume	Group A	239 ± 42.5	230 ± 33.5	226 ± 21.5	0.001	S
	Group B	240 ± 37.5	240 ± 36.5	240 ± 27.5	0.34	NS
	MD	-1	-10	-14		
	P-value	0.32	0.03	0.002		
	Sig	NS	S	S		

$\bar{X}$: Mean, SD: Standard deviation, MD: Mean difference, p value: Probability value
S: Significant, NS: Non-significant.

DISCUSSION

Heart failure has been addressed as a crucial health threat for both genders worldwide, as well it has a significantnegative impact on sufferers' quality of life, in addition to exhausting healthcare systems due to frequent patients painful complains, their functional impairments those considered a life-threating issue [3]. Moreover, CHF is acharacterized by an enormous individual and socioeconomic influences, as well comprehensive evaluation individuals had ensured that their left ventricular ejection fraction (LVEF), which required a clear vision in rehabilitation stream to emphasize the importance of addressing rehabilitation through distinguishing class of heart failure clinically [17]. Earlier clinical guidelines for management of heart failure had been emphasized on the importance of regaining homeostatic control through the ANS [18]. Moreover, obvious vagus nerve stimulation using transcutaneous electrical stimulation has oriented recently most of clinicians and academic researchers for ensuring importance of regaining, also preserving cardiac muscle functioning in whom suffering from CHF [19]. Current study results were supported by previous enumerated epidemiological point of view in the literature review correlated with what results` of the present study analysis show regarding the enormity of this burden is expected to continue to grow chronic heart failure as a major public health concern that ensured via reported prevalence and hospitalizations. As well our study is supported by the report of Sharma et al [20] who had stated that progressive chronic heart failure with unclear explanations there is an autonomic imbalance with increase in sympathetic and renin–angiotensin–aldosterone system activity and withdrawal of parasympathetic efferent activity. Current study results revealed that there was a significant increase in the 6MWT of group A compared with that of group B after 1st session (p 0.02), also revealed a significant increase in the 6MWT of group A compared with that of group B post treatment (p 0.001).

Current study results were supported by a recent published work by Yokota [21]. Those ensured that higher the frequency, stronger afferent vagal nerve signal transmission is superior for gaining more improvements, also the relation between the duration of stimulation and the effectiveness of tVNS was noticed in reducing the heart rate. Yokota and colleagues suggested that gaining an effective and optimal dose in clinical application of tVNS, specific stimulus parameters and sex differences should be taken into consideration including a stimulation frequency of 100 Hz, current intensity of 3.0 mA, and over 250 μs to improve overall clinical outcomes among chronic heart failure population.

The recorded improvement in functional disability among chronic heart failure participants could be explained based on negative chronotropic (reduction in heart rate), dromotropic (reduction in atrioventricular conduction), and inotropic (reduction in ventricular contractility) actions as ensured previously by Capilupi et al. [22] plus cervical vagus nerve have strengthened the possibility of selective electrical neuromodulation with minimal side effects andenhanced organ selectivity [23].

As well, current study results revealed that there was a significant improvement according to MLHFQ of group A compared with that of group B after 1st session, and post treatment (p 0.01). In agreement with current study findings, some evidence has stated that tVNS therapeutic approaches led to inhibited the increased secretions in whom suffering from cardiac lesions such as heart failure, thus results in activation of the cholinergic anti-inflammatory pathway (CAP) by the efferent vagal nerve causes the release of ACh that chains with the α7 nicotinic ACh receptors (α7nAChR) of macrophages, which inhibits the secretions of pro- inflammatory products like TNF-α, which slow down cardiac affection progression according to Wang et al [24].

However, On the other hand, recent clinical trial had reported that although VNS is safe and a widely tolerable therapeutic approach, some minor side effects have been observed as concluded, also by Yap et al [25].

In disagreement with our results, earlier clinical trial conducted by Poppa [26]. had ensured that VNS neuromodulation in humans involves the insula and functionally related regions, where VNS` known side effects were reported in several studies as pain and tingling at the site of stimulation. In the same line, an earlier clinical trial conducted by Dali et al [27]. had presented a 62% reduction in side effects for cardiac modulation in sheep use of tVNS showcases a shift of the vagus towards parasympathetic balance.

Also, regarding treatment effect on heart muscle function assessed via echo 'EF, ESV, and EDV' among group A has stated that the means ± SD value pretreatment of heart muscle function (EF, ESV, and EDV), pretreatment of group A were 38 (35-40), 148 ± 30.5 and 239± 42.5, and after 1st session were 41 (37-43), 135 ± 25.5 and 230 ± 33.5, where at post treatment was 44 (38-46), 130 ± 20.5, and 226 ± 21.5. The mean difference between pre and post treatment was -6, 18, and 13 degrees. There was a significant improvement in heart muscle function of group A post treatment compared with pretreatment (p 0.001). Furthermore, the mean ± SD value of heart muscle function pretreatment of group B were 37 (35-41), 151 ± 35.5 and 240 ± 37.5, and after 1st session was 37 (36-41), 151 ± 32.5 and 240 ± 36.5, where at post treatment was 37 (36-41), 150 ± 25.5, and 240 ± 27.5. There was a significant increase in heart muscle function of group B post treatment compared with pretreatment (p 0.001).

In agreement with current study findings, some evidence has stated that tVNS therapeutic approaches led to exert prominent adrenergic also anti-inflammatory benefits those could be accomplished transcutaneous by stimulating the auricular branch of the vagus nerve that associated with a favorable change in sympatho-vagal balance, which provides clinical improvement to chronic heart failure individuals according to Fallgatter et al [28].

On the other hand, recent clinical trial had reported that although VNS might activation of the ipsilateral nucleus tractus solitarius, which is the first central relay of vagal afferents, resulting in stimulation of higher order vagal projections in the brainstem and forebrain as concluded by Frangos et al [29].

In disagreement with our results, earlier clinical trial conducted by Clancy et al [15]. that had ensured that VNS might enhance parasympathetic tone and decreasing sympathetic tone, particularly among patients with atrial fibrillation.

Finally, regarding the participants` effect of treatment on 6MWT, MLHFQ and heart muscle function via non- invasive echocardiogram (echo) to assess ejection fraction (EF), end-systolic volume (ESV), and end-diastolic volume (EDV), using the same speckle-tracking

algorithm as outcome measures. There was a significant interaction effect of treatment and time (p 0.001). There was a significant main effect time (p 0.001). Unless, there was a significant main effect of treatment (p 0.001).

Pavlov et al [30]. had ensured that VNS at cervical region has been established as a nonpharmacologic therapeutic approach for control of inflammation in a number of pre-clinical disease models. Finally, there are limited literature on similar interventional clinical trials, could ensure an immediate effectiveness of tVNS application on outcome measures, but restricted of major limitation of current study was that short- and long- term effectiveness of tVNS on functional capability andcardiac muscle function cumulative effect among heart failure patients. Furthermore, clinical recognition of tVNS technique that could be more superior in managing heart failure population either male or female on an extended follow up.

CONCLUSION

Based on current study revealed results and we could conclude that non-invasive vagus nerve stimulation (tVNS) is a safe and effective method , improving functional capacity, health-related quality of life and heart muscle function in chronic heart failure by transcutaneous electrical stimulation.

Conflict of interest

The authors confirmed that this article content has noconflict of interest.

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