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Research paper

# Sudarshan Kriya Yoga improves cardiac autonomic control in patients with anxiety-depression disorders

Edgar Toschi-Dias[a,b,c], Eleonora Tobaldini[b,c], Monica Solbiati[b,c], Giorgio Costantino[b,c], Roberto Sanlorenzo[d], Stefania Doria[d], Floriana Irtelli[d], Claudio Mencacci[d], Nicola Montano[b,c,*]

[a] Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil
[b] Department of Internal Medicine, Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlínico, Milan, Italy
[c] Department of Clinical Sciences and Community for Health, University of Milan, Milan, Italy
[d] Department of Neuroscience, "Fatebenefratelli e Oftalmico" Hospital, Milan, Italy

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ABSTRACT

*Background:* Several studies have demonstrated that adjuvant therapies as exercise and breathing training are effective in improving cardiac autonomic control (CAC) in patients with affective spectrum disorders. However, the effects of Sudarshan Kriya Yoga (SKY) on autonomic function in this population is unknown. Our objective was to test the hypothesis that SKY training improves CAC and cardiorespiratory coupling in patients with anxiety and/or depression disorders.

*Methods:* Forty-six patients with a diagnosis of anxiety and/or depression disorders (DSM-IV) were consecutively enrolled and divided in two groups: 1) conventional therapy (Control) and 2) conventional therapy associated with SKY (Treatment) for 15 days. Anxiety and depression levels were determined using quantitative questionnaires. For the assessment of CAC and cardiorespiratory coupling, cardiorespiratory traces were analyzed using monovariate and bivariate autoregressive spectral analysis, respectively.

*Results:* After 15-days, we observed a reduction of anxiety and depression levels only in Treatment group. Moreover, sympathetic modulation and CAC were significantly lower while parasympathetic modulation and cardiorespiratory coupling were significantly higher in the Treatment compared to Control group.

*Conclusions:* Intensive breathing training using SKY approach improves anxiety and/or depressive disorders as well as CAC and cardiorespiratory coupling. These finding suggest that the SKY training may be a useful non-pharmacological intervention to improve symptoms and reduce cardiovascular risk in patients with anxiety/depression disorders.

## 1. Introduction

Besides being common lifelong, affective spectrum disorders are some of the most burdensome diseases with respect to their global impact on morbidity, mortality, and loss of quality of life (Baxter et al., 2013; De Wilde et al., 2007; Pavlova et al., 2015; Waraich et al., 2004). While many mechanisms have been proposed, attention to autonomic dysfunction remains of interest for several researches (Taylor, 2010; Voss et al., 2011). The polyvagal theory has emerged as an important explanatory construct for a wide range of psychiatric conditions and provides a new perspective by emphasizing the phylogeny of the autonomic nervous system (Porges, 2007, 2009). According to this theory, the myelinated vagal fibers originating in the nucleus ambiguous may mediate the relationship between autonomic dysfunction and altered social behavior in patients with mood disorders (Beauchaine et al., 2007).

From this point of view, the cardiorespiratory coupling is an important physiological mechanism and has been largely associated with cardiac vagal modulation (Bar et al., 2008; Peupelmann et al., 2009). Beside the mechanical interaction due to the coupling between the systemic and pulmonary circulations during breathing, cardiac and respiratory systems are closely linked by neuronal pathways through overlapping brainstem networks that modulate the autonomic nervous system and are essential for survival (Dick et al., 2014). During inspiration the pulmonary stretch receptors are stimulated and this information is transmitted via pulmonary C-fiber afferents to medullary nuclei of central integration that reflexively inhibit the cardiac vagal efferent activity causing the shortening of the R-R interval (RRi). In contrast, during expiration this signaling is abolished and the activity of the efferent cardiac vagal nerve is stimulated due to central integration between cardioinhibitory reflexes (i.e. arterial baroreflex)

* Correspondence to: Ospedale Maggiore Policlinico, Via Francesco Sforza, 28, Milan, Italy.
*E-mail address:* nicola.montano@unimi.it (N. Montano).

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causing the extending the RRi (Dick et al., 2014; Yasuma and Hayano, 2004).

It has been documented that elevated levels of anxiety alters the parameters of the breathing pattern, eliciting increased respiratory rate and tidal volume and decreased respiratory time in healthy individuals (Mador and Tobin, 1991; Masaoka and Homma, 1997). In addition, due to the high prevalence of metabolic abnormalities such as obesity, diabetes and dyslipidemia (Teixeira and Rocha, 2007; Vancampfort et al., 2015), patients with mood disorders have autonomic dysfunction and reduced cardiorespiratory coupling (Bar et al., 2010; Berger et al., 2011; Voss et al., 2011) which increases the risk of cardiovascular disease.

On the other hand, several studies have demonstrated that adjuvant therapies such as physical exercise and breathing training are effective in improving cardiac autonomic control (CAC) in patients with affective spectrum disorders (Booij et al., 2015; Brown and Gerbarg, 2005). Based on Yoga techniques, it has been consistently shown that breathing exercises have beneficial effects on CAC and breathing function (Santaella et al., 2011), enhance cardiorespiratory adaptation to hypoxia (Bernardi et al., 2007) and improve mood state (Pascoe and Bauer, 2015).

Sudarshan Kriya Yoga (SKY) is a comprehensive program based on some yoga techniques that includes bodily postures, powerful breathing exercises and meditation (Janakiramaiah et al., 1998). Briefly, the what particularly differentiate SKY form other Yoga-based interventions is a set of three sequencial breathing technique, Ujjiay – slow and forced breathing, 3 cycles per minute; Bhastrika – rapid exalation at 20–30 cycles per minute; Sudarshan Kriya – rhythmic, cyclical breathing of slow, medium, fast cycles (Brown and Gerbarg, 2005). Besides being an approach safe and low-cost, several evidences support which SKY can be a beneficial adjunct to the treatment of stress, anxiety and depression (Brown and Gerbarg, 2005; Doria et al., 2015). However, the effects of SKY on autonomic function in patients with anxiety and/or depression disorders is unknown. To answer this question, the objective of this research was to evaluate the effects of intensive breathing by SKY training on CAC and cardiorespiratory coupling.

## 2. Methods and materials

### 2.1. Subjects

We selected forty-six patients with a primary diagnosis of anxiety and/or mood disorders recruited (Doria et al., 2015) from the Department of Mental Health and Neurosciences of the Fatebenefratelli and Ophthalmic Hospital. These patients were diagnosed with anxiety and/or mood disorders according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association, 1994). All the patients were under stable pharmacological treatment for at least 6 months and patients in which pharmacological treatment not working were excluded from the study. All the patients were free of any cardiovascular, metabolic and respiratory comorbidities (such as hypertension, coronary artery diseases and diabetes). Twenty-five patients (54%) were diagnosed with generalized anxiety disorder, ten (22%) with dysthymic disorder or depressive disorders not otherwise specified, and the remaining eleven (24%) with both dysthymic and generalized anxiety disorder. Then, the enrolled patients were divided in two groups: 1) conventional therapy (Control, n=22) and conventional therapy associated with SKY breathing for 15 days (Treatment, n=24). To evaluate the severity of anxiety and mood symptoms and monitor response to treatment, Hamilton rating scale for anxiety (HRSA) and depression (HRSD) and Symptom Checklist-90 (SCL-90) were applied at baseline (T0) and after 15 days (T1) (Doria et al., 2015). This study was approved by local Ethics Committee in accordance with the principles outlined in the Declaration of Helsinki and written informed consent was obtained from each patient prior to the study.

### 2.2. Psychological evaluation

The severity of anxiety, depression and distress symptoms were evaluated by a clinical psychologist experienced in the application and correction of the relevant tools in T0 and T1 periods (Hamilton and White, 1959; Hamilton, 1960; Derogatis and Cleary, 1977). The anxiety and depression levels were assessed by the Hamilton rating scale for anxiety (HRSA) and depression (HRSD), which consists of two independent questionnaires with 14 and 21 items rated on a scale of 0–4, respectively (Hamilton and White, 1959; Hamilton, 1960).

To assess the level of psychological distress we use the Symptom Checklist-90 (SCL-90). The SCL-90 is a well-established self-report instrument which consists of 90 questions on a scale of 0–4 that measure 9 symptoms of psychological dimensions (depression, anxiety, phobic anxiety, hostility, obsessive-compulsive, interpersonal sensitivity, somatization, paranoid ideation and psychoticism) (Derogatis and Cleary, 1977). The level of psychological distress was obtained by means of the Global Symptom Index (GSI) (Hamilton and White, 1959; Hamilton, 1960).

### 2.3. Data acquisition

In order to evaluate the cardiac autonomic control, subjects underwent the recording of ECG (lead II) and respiratory movements using a thoracic piezoelectric belt. We used a telemetric device to record the ECG and respiration (BT-16 Plus; FM, Monza, IT) during 10 min rest period. These signals were collected at both T0 and T1 periods and stored in real-time in a computer using an analogical-digital converter with resolution of 16 bits and sampling frequency of 250 Hz for subsequent remote data analysis according to international guidelines (Task Force, 1996).

### 2.4. Data analysis

#### 2.4.1. Cardiac autonomic control

Data of heart and respiratory rate were imported and analyzed in a software (HeartScope II; AMPS-LLC, New York, USA) on a personal computer by a trained investigator (ETD). Briefly, R-waves were detected and marked to extract the time series of RRi and we used parabolic interpolation of R peak to ectopic beats or artifacts correction. The time series of spontaneous breaths (RESP) was extracted once for every cardiac cycle in correspondence with R-waves. To evaluate cardiac autonomic control, the times series of RRi and RESP on stationary segments of 250–300 beats were analyzed by an autoregressive frequency domain approach. This procedure enables the automatic quantification of the center frequency (ω) and the power of oscillatory component in low (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.40 Hz) ranges (Montano et al., 1994, 2009). LF and HF components can be expressed both in absolute and in normalized units (nu). The normalization procedure was obtained by calculating the percentage of the LF and HF band with respect to the total power after subtracting the power of the very-low-frequency component (frequencies $< 0.04$ Hz). The ratio of LF and HF of RRi can be calculated as well.

The LF component in normalized units represents an index of sympathetic cardiac modulation and LF/HF an index of sympathovagal balance (Montano et al., 1994, 2009). In the current study, we considered LF/HF as an index of cardiac autonomic control. According to international guidelines, healthy individuals under resting conditions show LF/HF values of less that 2.0 (Task Force, 1996) and the higher this index in resting condition, the worse the cardiac autonomic control.

#### 2.4.2. Cardiorespiratory coupling

The cross-spectral analysis was performed by means of bivariate autoregressive approach with model order was fixed to 10 (Barbic et al.,

2015) using HeartScope II program (AMPS-LLC, New York, USA). This procedure permits the quantification of gain, phase (Φ) and coherence ($K^2$) between different signal variabilities. The gain of the transfer function quantifies the intensity of the response of the output signal (RRi) per unit of spontaneous change of the input signal (RESP), while the phase measures the time lag between these signals. The function of $K^2$ measures the degree of linear coupling between RRi and RESP at the same frequency in both variability signals. In the present study, the cardiorespiratory coupling was quantified by means of $K^2$ index in the central frequency (ω) within HF range (0.15–0.40 Hz) and expressed in percentage units (Montano et al., 1994; Patruno et al., 2014).

### 2.5. Breath intervention program

As previously described (Doria et al., 2015), the breath intervention program in the current study was based on SKY. The sequence of SKY method was adapted and validated to clinical purposes for this population in which consists of light yoga postures and five sequential breathing exercises separated by 30/60-s periods of normal breathing and observation of physical sensations and breath; in particular the SKY technique consists of variations among slow, medium and fast cycles separated by 30-second periods of normal breathing (Doria et al., 2015). Thus, the patients of Treatment group were submitted to an intense SKY workshop during 10 sessions of approximately two hours/day distributed in two consecutive weeks. On the other hand, the patients allocated to the Control group were instructed on the importance of adherence to pharmacological and psychotherapeutic treatment and were re-evaluated after 15 days.

### 2.6. Statistical analysis

The data are presented as median and inter-quartile ranges. A chi-square ($\chi^2$) was used to assess categorical data differences. For each variable, the Lèvene and Shapiro-Wilk tests were used to assess the homogeneity and normality of distribution, respectively. Demographic, psychometrics and autonomic data were compared using Student's *t*-tests. However, Wilcoxon or Mann-Whitney tests were used when appropriate. Probability values of $P < 0.05$ were considered statistically significant.

## 3. Results

The demographics, diagnostic, psychopathological and psychometric characteristics of the study population are summarized in Table 1. Age, gender, heart rate, prevalence of anxiety and/or depression disorders, HRSA and GSI/SCL-90 were similar between groups. Moreover, Control group showed higher HRSD and proportion of patients using bezodiazepines than Treatment group (Table 1).

Baseline data of CAC and cardiorespiratory coupling in patients with anxiety and/or depression disorders are shown in Table 2. LFnu, marker of sympathetic modulation, HFnu, marker of parasympathetic modulation and LF/HF, index of the sympatho-vagal balance, were similar between groups. However, the total variance was significantly lower and the cardiorespiratory coupling ($K^2_{HF}$) significantly higher in the Treatment group compared to the Control group (Table 2).

The effects of SKY therapy on psychological symptoms in patients with anxiety and/or depression disorders are presented in Table 1. In the Treatment group, SKY training significantly reduced the levels of anxiety, depression and distress symptoms when compared to baseline (Table 1). After 15 days, the Treatment group showed lower levels of anxiety and distress symptoms when compared to Control group. In the Control group, the level of psychological distress was significantly lower when compared to baseline (Table 1). The effects of SKY therapy on cardiac autonomic control in patients with anxiety and/or depression disorders are shown in Fig. 1.

**Table 1**
Demographic, psychopathological and psychometric characteristics of patients with anxiety and/or mood disorders.

| | Control (n=22) | Treatment (n=24) |
|---|---|---|
| **Demographics** | | |
| Age (years) | 44 [32–51] | 44 [44–49] |
| Gender (M/F) | 8/14 | 9/15 |
| Heart rate (bpm) | 69 [61–88] | 73 [66–84] |
| **Diagnostic** | | |
| Anxiety Disorders (%) | 45 | 63 |
| Depression Disorders (%) | 32 | 13 |
| Anxiety and Depression Disorders (%) | 23 | 25 |
| **Psychopharmacological** | | |
| SSRI (%) | 64 | 58 |
| Citalopram# (mg) | [20–20] | [20–20] |
| Escitolapram# (mg) | [20–25] | [10–20] |
| Fluoxetine# (mg) | [20–20] | – |
| Fluvoxamine# (mg) | – | [200–200] |
| Paroxetine# (mg) | [10–20] | [10–20] |
| Sertraline# (mg) | – | [50–50] |
| Venlafaxine# (mg) | [75–75] | – |
| SNRI (%) | 14 | 8 |
| Amitriptyline# (drops) | – | [15–15] |
| Duloxetine# (mg) | [60–60] | – |
| Benzodiazepines (%) | 50 | 4* |
| Alprazolam# (mg) | [0.5–0.5] | [0.5–0.5] |
| Bromazepam# (mg) | [3–3] | – |
| Clonazepam# (drops) | [15–15] | – |
| Delorazepam# (drops) | [10–18] | – |
| Etizolam# (drops) | [10–10] | – |
| Prazepam# (drops) | [10–10] | – |
| Triazolam# (mg) | [125–125] | – |
| Antiepileptic (%) | 5 | 4 |
| Pregabalin# (mg) | [75–75] | [20–20] |
| Antipsychotics (%) | 9 | – |
| Haloperido# (drops) | [20–20] | – |
| Promazine# (drops) | [20–20] | – |
| Mood stabilizer (%) | 5 | – |
| Lithium# (drops) | [5–5] | – |

| **Psychometrics** | **T0** | **T1** | **T0** | **T1** |
|---|---|---|---|---|
| HRSA | 19 [15–23] | 19 [14–25] | 18 [15–22] | 12 [7–17]†‡ |
| HRSD | 20 [13–23] | 20 [14–22] | 13 [10–16]* | 9 [6–11]†‡ |
| GSI/SCL-90 | 2.4 [2.0–3.1] | 2.0 [1.7–2.6]† | 2.1 [1.7–3.1] | 0.9 [0.5–1.2]†‡ |

Median [interquartil ranges]; #=Range [min-max]; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors; GABA-R=GABA(A) receptors; HRSA=Hamilton rating scale for axiety; HRSD=Hamilton rating scale for depression; GSI/SCL-90=Global score index of symptom checklist-90.
*=difference vs. Control group in T0 period, $P < 0.05$.
†=difference vs. Treatment group in T1 period, $P < 0.05$.
‡=difference vs. Control group in T1 period, $P < 0.05$.

As to the effects of the SKY therapy, in the Treatment group, at T1, Variance was significantly increased as compared to T0 (Fig. 1, Panel A), as well as HFnu, (Fig. 1, Panel C); on the contrary, LFnu, was reduced at T1 as compared to T0 (Fig. 1, Panel B) as well as sympatho-vagal balance (Fig. 1, Panel D). No significant changes in CAC were found in the Control group between T0 and T1.

The interesting finding is that SKY therapy improves cardiorespiratory coupling ($K^2_{HF}$) in patients with anxiety and/or depression disorders (Fig. 2, Panel B) after 15 days of treatment. Moreover, no significant changes were found in the Control group over the 15-days duration of the study.

**Table 2**
Baseline measures of spectral parameters calculated by linear method using autoregressive model of patients with anxiety and/or mood disorders.

| | Control (n=22) | Treatment (n=24) | *P* |
|---|---|---|---|
| **R-R interval** | | | |
| Variance ($ms^2$) | 1384 [748–2316] | 692 [552–1366] | 0.03 |
| LF nu | 67 [51–78] | 47 [35–78] | 0.14 |
| HF nu | 27 [16–45] | 48 [18–58] | 0.07 |
| LF/HF | 2.7 [1.2–4.3] | 1.0 [0.6–4.3] | 0.14 |
| **RESP-RRi** | | | |
| $\omega_{HF}$ (Hz) | 0.28 [23–33] | 0.25 [0.210.31] | 0.38 |
| $K^2_{HF}$ (%) | 64 [53–76] | 87 [65–93] | < 0.01 |

Median [interquartil ranges]; RRi=R-R interval; RESP=respiration; LF=low frequency; nu=normalized unit; HF=high frequency; LF/HF=sympathovagal balance; ω=central frequency; $K^2$=coherence.

## 4. Discussion

The major findings of this investigation are that intensive breathing training using the SKY approach i) reduces the level of anxiety and depression symptoms and ii) improves CAC, increases cardiorespiratory coupling.

These results confirm the antidepressant effects of the SKY method, previously reported in patients with affective spectrum disorders (Doria et al., 2015; Janakiramaiah et al., 2000; Vedamurthachar et al., 2006). In a prospective randomized controlled trial, Janakiramaiah et al. demonstrated that SKY approach promoted a 67% remission rate of clinical symptoms after four weeks of intervention in patients' severe melancholic depressives (Janakiramaiah et al., 2000). In addition, we previously observed that the SKY treatment was able to reduce anxiety and depression symptoms in patients affected by generalized anxiety disorder, with or without comorbidities (Doria et al., 2015). The mechanisms involved in the reduction of mood symptoms by SKY are out of the scope of the present study. However, several mechanisms could be hypothesized. Vedamurthachar et al. observed an improvement of depressive symptoms promoted by the SKY treatment during the detoxification phase in subjects with alcoholism, associated with the reduction of cortisol and ACTH levels (Vedamurthachar et al., 2006). This idea is reinforced by the recent findings of Naveen et al. (2016) who showed that beyond the reduction of cortisol levels, 3-months of Yoga therapy increased the levels of serum Brain Derived Neurotrophic Factor (BDNF) in patients with major depression. Thereby, based on these findings, intensive breathing training using the SKY procedure may be a strategy non-pharmacological safe and of low-cost with potential beneficial to the treatment of stress, anxiety and depression.

Regarding the autonomic effects of SKY, we found that intensive breathing training improves CAC, with a reduction in cardiac sympathetic modulation and an increased in cardiac parasympathetic modulation in patients with anxiety and/or depressive disorders. As far as we know, similar effect on cardiac autonomic functions was demonstrated in elderly subjects (Santaella et al., 2011) and diabetic patients (Jyotsna et al., 2013). Thus, the present study provides for the first time evidence that intensive breathing training using SKY approach improves CAC in patients with anxiety/depression disorders. Neuroimaging studies using functional magnetic resonance image had demonstrated that a variation in the respiratory rhythm will

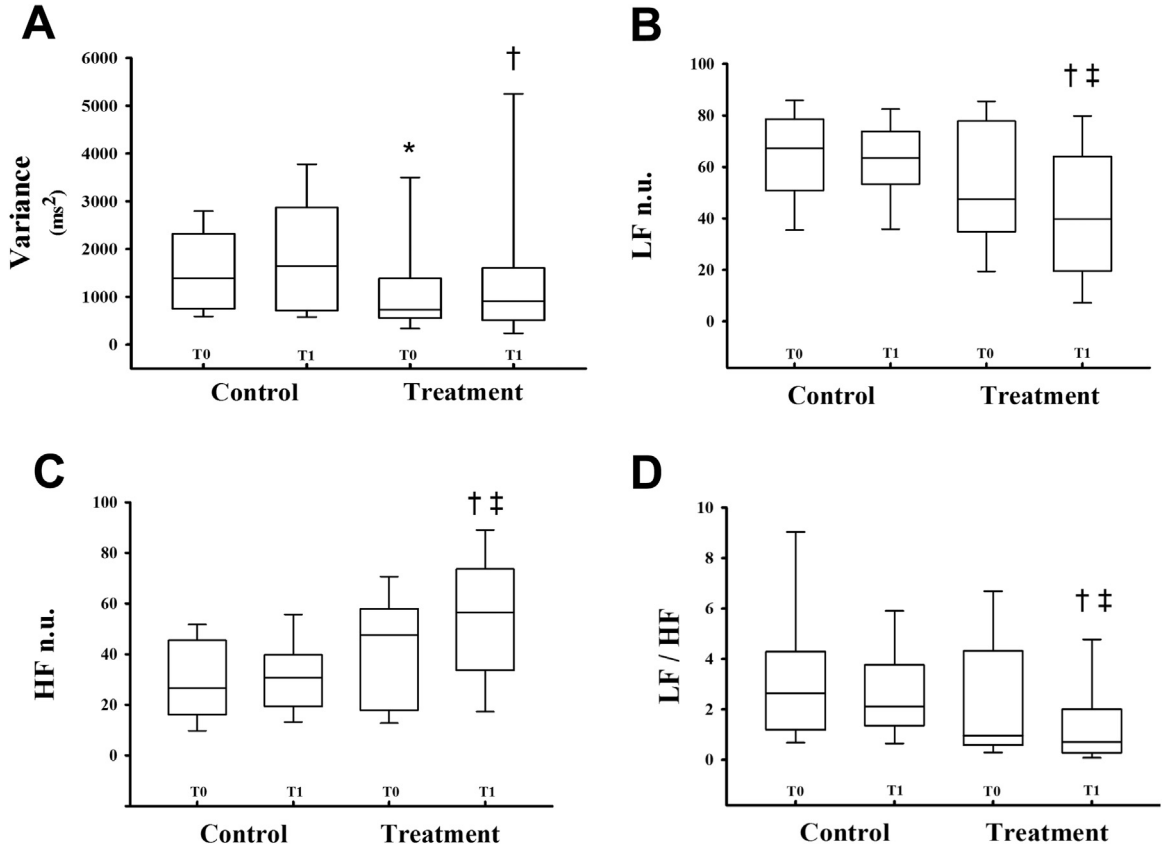


**Fig. 1.** Variance of R-R intervals (Variance, Panel A) expressed in square milliseconds; cardiac sympatho-vagal balance (LF/HF, Panel B); oscillatory components of low (LF, Panel C) and high-frequency of R-R intervals (HF, Panel D) expressed in percentage values in patients with mood disorders in the Control and Treatment groups in T0 and T1periods. Note that Variance was lower in T0 period and that SKY therapy increased the level of Variance of R-R intervals (Panel A) in Treatment group. In addition, SKY therapy reduced LF/HF (Panel B) and LF (Panel C) and increased HF (Panel D) in the Treatment group. And, after intervention, LF/HF (Panel B) and LF (Panel C) were lower and HF (Panel D) was higher in Treatment group when comparison with Control group. *=difference vs. Control group in T0 period, $P < 0.05$; †=difference vs. Treatment group in T1 period, $P < 0.05$; ‡=difference vs. Control group in T1 period, $P < 0.05$.

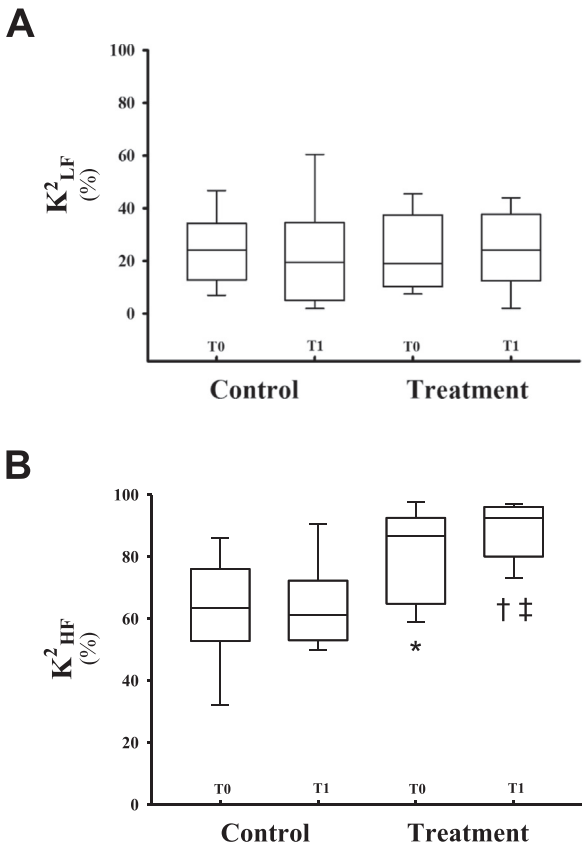


**Fig. 2.** Cardiorespiratory coupling in low frequency ($K^2_{LF}$, Panel A) and high frequency ranges ($K^2_{HF}$, Panel B) expressed in percentage values in patients with mood disorders in the Control and Treatment groups in T0 and T1periods. Note that Treatment group showed higher $K^2_{HF}$ (Panel B) that Control in T0 period. After 15-days, $K^2_{HF}$ (Panel B) significantly increased only in the Treatment group. *=difference vs. Control group in T0 period, $P < 0.05$; †=difference vs. Treatment group in T1 period, $P < 0.05$; ‡=difference vs. Control group in T1 period, $P < 0.05$.

translate into changes in the neural activity of brainstem (Liou et al., 2005). Additionally, it is well known that CAC is mediated by inhibitory parasympathetic cholinergic neurons located in the brainstem and stimulatory sympathetic noradrenergic neurons. Thus, we believe that the combination of different frequencies, intensities and respiratory rhythms by means of Yoga techniques creates a variation of physiological stimuli that modulates the reflex response with an increase in the vagal efferent and an inhibition in the sympathetic efferent activity, ultimately resulting in an improvement of the cardiac autonomic control. This shift in central sympathovagal balance might per se improve the anxiety/depression symptoms, modifying the relationship between serotoninergic, noradrenergic and cholinergic transmissions (Pervanidou and Chrousos, 2010; Mesulam et al., 1992).

Accumulated evidences show that cholinergic phenotype of brainstem autonomic neurons is promoted by BDNF (Yang et al., 2010; Zhou et al., 2004). Moreover it is known that the BDNF variant may play a key role in the genetic predisposition to anxiety and depressive disorders (Chen et al., 2006). In a recent study, Wan et al. demonstrated that BDNF knockout mice exhibit elevated resting heart rates, and the infusion of BDNF intracerebroventricularly reduces heart rate with a slower acting and negative chronotropic effect on heart rate that is sustained for several hours after a single bolus infusion (Wan et al., 2014). However, we cannot rule out the role of central and peripheral chemosensitivity as important modulators of the autonomic and ventilatory control based on the findings of this study. Spicuzza et al. (2000) demonstrated that yoga trainees showed a lower ventilatory response to hypoxia and hypercapnia during spontaneous breathing. This finding suggests that yoga trainees have major tolerance to gas exchange and this effect has a clinical implication, since central and peripheral chemoreflex hypersensitivity is associated with major mortality in patients with heart failure (Giannoni et al., 2009).

Furthermore, the present study extends the knowledge about the mechanisms involved in the improvement in CAC by the SKY training in this population. The other novelty of the current study is that intensive breathing by the SKY training increases the spontaneous cardiorespiratory coupling in patients with anxiety and/or depression disorders. In health individuals, Bhavanani et al. observed that the slow deep breathing (pranava pranayama) promotes a higher effect in respiratory sinus arrhythmia. Yet, each yogic breathing technique (pranayama) promotes different responses in the amplitude of respiratory sinus arrhythmia (Bhavanani et al., 2016). To our knowledge, this is the first investigation that reports a beneficial effect about cardiorespiratory coupling in patients with anxiety and/or depressive disorders. Due to respiratory modulation by means of interaction of brainstem neurons involved in CAC, we can speculate that the improvement of sympatho-vagal balance and the increase of cardiorespiratory coupling promoted by SKY training may be, at least in part, considered as an indicator of improvement in neural plasticity, but further ad hoc studies are needed to confirm this hypothesis.

Interestingly, the Control group showed a lower cardiorespiratory coupling as compared to the Treatment group at T0 period. Nonetheless, this finding should be interpreted cautiously. We believe that this result might be due to the effect of the drugs used by these patients, such as anticholinergics and neuroleptics. Namely, it has been documented that some serotonin reuptake inhibitor increased the vagal modulation and cardiorespiratory coupling (Bar et al., 2010; Pizzi et al., 2011). However, the use of tricyclic antidepressants (Kemp et al., 2010), serotonin and norepinephrine reuptake inhibitor (Chang et al., 2012) and benzodiazepines would decrease the vagal modulation and cardiorespiratory coupling (Adinoff et al., 1992; Agelink et al., 2002). In fact, the use of benzodiazepines was higher in the Control than in the Treatment group. Several evidences showed that benzodiazepines promote vagolytic effects probably through their interaction with the GABA-receptor/chloride ion channel complex (Adinoff et al., 1992; Agelink et al., 2002). Thus, our data highlight the need to implement non-pharmacological strategies that increase the cardiorespiratory coupling, mainly in patients with anxiety and/or depressive disorders.

The present study has some strengths and limitations. The major limitation of our study is that this is not a randomized controlled trial. However, even though all patients were stable and under the same therapy for at least 6 months before being allocated to the groups, the level of depression makes the groups clinically different at the beginning of the study. Interestingly, this bias may suggest a new perspective for the SKY approach. Despite pharmacological advances, 15–30% of depressed patients are refractory to treatment (Berlim and Turecki, 2007). Thus, this patient profile may benefit from the association between conventional treatment and SKY, but more research are needed. On the other hand, the homogeneity of the study population, which is free of any cardiovascular, metabolic and respiratory comorbidities (such as hypertension, coronary artery diseases and diabetes), strengthens our findings about the real effect of SKY treatment in this population.

In conclusion, intensive breathing training using the SKY approach improves CAC and cardiorespiratory coupling in patients with anxiety and/or depression disorders. These findings suggest that the SKY training may be a non-pharmacological intervention to reduce cardiovascular risk in these patients.

## Trial registration

Clinical Trials NCT02828072 (https://clinicaltrials.gov/show/NCT02828072).

## Conflict of interest

The authors declare no conflict of interest.

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