

Biofeedback Assisted Control of Respiratory Sinus Arrhythmia as a Bibehavioral Intervention for Depressive Symptoms in Patients After Cardiac Surgery: A Preliminary Study

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Abstract The current study investigated whether biofeedback training aimed at increasing respiratory sinus arrhythmia (RSA), a measure of cardiac vagal modulation, can reduce depressive symptoms in patients after cardiac surgery. This randomized controlled study enrolled 26 patients after first-time cardiac surgery. The patients were randomly assigned to an RSA-biofeedback group ($N = 13$) or to a treatment as usual group ($N = 13$). The biofeedback training consisted of five 45 min sessions designed to increase RSA. The outcome was assessed as changes in RSA and in the Centre for Epidemiologic Studies of Depression (CES-D) values from pre- to post-training. Both groups were comparable for demographic and biomedical characteristics. RSA increased significantly in patients who underwent RSA-biofeedback compared to controls. Moreover, the CES-D scores were reduced significantly from pre- to post-training in the RSA-biofeedback group compared to the controls. Changes in RSA were inversely related to changes in CES-D scores from pre- to post-training. These findings extend the effectiveness of RSA-biofeedback for increasing vagal modulation as well as for reducing depressive symptoms in post-surgical patients. Overall, the current study also suggests that this bibehavioral intervention may add to the efficacy of postoperative risk reduction programs and rehabilitation protocols in cardiac surgery patients.

Keywords Cardiac surgery · Depressive symptoms · Parasympathetic nervous system · Respiratory sinus arrhythmia · Vagal tone

Introduction

Undergoing cardiac surgery is a significant life event with a relevant impact on the affective status of patients. High rates of depression and anxiety are reported in 25–30 % of patients undergoing cardiac surgery (Langeluddecke et al. 1989; McKhann et al. 1997). Specifically, Langeluddecke et al. (1989) reported that 36 % of patients had a clinically significant score on the Center for Epidemiological Study of Depression scale (CES-D) (Radloff 1977) prior to coronary artery bypass surgery (CABG), whereas the incidence of anxiety measured with the Spielberger State Anxiety Inventory (STAI) (Spielberger et al. 1970) was approximately 30 %.

More importantly, preoperative depression may persist after cardiac surgery in up to 20 % of patients (Vingerhoets 1998). Evidence has shown that patients with postoperative depression are at greater risk for more cardiac morbidity and fatal cardiac events (Blumenthal et al. 2003; Connerney et al. 2001). Connerney et al. (2001) reported that major depressive disorder was an independent predictor of cardiac events in the 12 months after CABG even after controlling for other biomedical risk factors. In the largest study of depression as a risk factor for mortality in patients after cardiac surgery, Blumenthal et al. (2003) showed that patients with persistent (i.e., before as well as 6 months after CABG) mild or moderate to severe depression had a greater likelihood (i.e., more than twice) of death than those who were never depressed.

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The psychophysiological mechanisms underlying depression as a risk factor for cardiovascular disease, cardiac morbidity, and/or fatal cardiac events after surgery are still debated. Both behavioral (i.e., poor adherence to cardiac treatment regimen) and biological (i.e., increased platelet aggregation) factors have been proposed as possible explanations. However, the strongest evidence implicates attenuated cardiac autonomic tone in the development of cardiovascular diseases (Carney et al. 1995a). Indeed, it is well-established that depression is related to dysregulation of the hypothalamic pituitary-adrenal axis and increased sympathetic nervous system activity (Siever and Davis 1985; Veith et al. 1994). Elevated sympathetic and/or reduced parasympathetic nervous system activities, in turn, have also been associated with ventricular fibrillation, ventricular tachycardia, and sudden cardiac death in patients with coronary artery disease (Podrid et al. 1990; Pruvot et al. 2000).

Respiratory sinus arrhythmia (RSA) has been widely used to assess cardiac autonomic modulation (Berntson et al. 1997; Grossman and Taylor 2007). RSA is a cardiorespiratory phenomenon characterized by heart rate (HR) fluctuation in phase with the respiration cycle (inhalation and exhalation): HR accelerates during inspiration and slows down during expiration. Specifically, RSA reflects the rhythmic increase and decrease of cardiac vagal efferent effects upon the sinoatrial node that are linked to respiration rate (Eckberg 2003; Hedman et al. 1995).

Several lines of evidence have documented that reduced RSA may be predictive of morbidity in individuals with cardiovascular diseases and may represent an index of poor vagal control as well as a marker of cardiovascular risk (Bigger et al. 1992; Hayano et al. 1990). Cross-sectional and longitudinal studies have also shown that reduced levels of RSA are linked to depression and/or depressive symptoms in nonsurgical populations (Balogh et al. 1993; Carney et al. 1995b). However, discrepant findings have also been reported regarding the relationship between RSA and depression (Carney et al. 1988; Khaykin et al. 1998). Possible reasons for these inconsistent findings involve the heterogeneity of individuals diagnosed with depression (Gotlib and Hammen 1992), small sample sizes, and the quantification of RSA without controlling for possible confounds such as respiration rate and depth (Grossman and Taylor 2007).

Pharmacological treatments of depression in patients with cardiovascular diseases and, to a major extent, in patients after cardiac surgery also represent a challenge. Indeed, with the exception of selective serotonin reuptake inhibitors (SSRIs) that are not contraindicated in patients with cardiovascular diseases, benzodiazepine, norepinephrine reuptake inhibitors, and tricyclic antidepressants can exert a vagolytic effect (Agelink et al. 2002), yielding to reduced heart rate variability (HRV) (Schroeder et al.

2002), or anticholinergic effects (Feighner 1999). Based on these findings, nonpharmacological treatments for depression in patients with coronary heart disease have been developed. There is evidence that cognitive behavioral interventions and interpersonal therapy can be effective in reducing depression (Lett et al. 2005). Interestingly, Carney et al. (2000) reported that cognitive behavioral therapy can also increase short-term HRV and reduce HR in severely depressed patients. However, in the largest study to date, while cognitive behavioral therapy was effective in lowering depression and increasing social support in patients after the onset of acute myocardial infarction, it failed to reduce cardiac morbidity and mortality (Berkman et al. 2003). Conversely, it is important to note that, although not mediated by change in depression, pharmacological therapy with SSRIs was associated with a reduction in risk of myocardial infarction, reinfarction and/or mortality. Specifically, the inhibitory effects of SSRIs on platelets have been implicated in reducing risk of myocardial infarction and/or mortality (Serebruany et al. 2001).

Although the effectiveness of psychological interventions for reducing risk factors related to coronary artery diseases is still debated (Lett et al. 2005), in the last two decades, several studies have reported that biobehavioral interventions such as biofeedback can be effective in reducing cardiovascular risk by enhancing vagal tone in patients with coronary heart disease (for a review, see Wheat and Larkin 2010). Specifically, Cowan et al. (1990) first reported that RSA-biofeedback training increased HRV and led to a better balance between sympathetic and parasympathetic activities in six cardiac patients. Del Pozo et al. (2004) extended this finding by showing that, compared to controls, RSA-biofeedback intervention increased HRV in patients with coronary heart disease six as well as 18 weeks after RSA training. More importantly, Nolan et al. (2005) reported that patients with coronary heart disease who had received five sessions of RSA-biofeedback showed increased parasympathetic HR modulation as well as reduced symptoms of depression compared to controls (i.e., without RSA-biofeedback).

Though there is increasing evidence that biofeedback interventions can enhance vagal modulation and, in turn, reduce symptoms of depression and cardiovascular outcome in patients with cardiovascular diseases, research has yet to investigate the potential effectiveness of RSA-biofeedback for increasing vagal tone for treating depressive symptoms in the context of rehabilitation after cardiac surgery. Accordingly, the aims of the present study were two-fold. First, we examined whether, compared to the treatment as usual (TAU), RSA-biofeedback plus TAU (RSA-biofeedback + TAU) increases vagal tone, as measured by RSA, in patients after first-time cardiac surgery. Second, we investigated whether increased vagal tone was

related to reduced depressive and anxiety symptoms in patients who had undergone cardiac surgery.

Methods

Participants

After local ethics committee approval, 33 consecutive patients (mean age = 60.7, $SD = 8.1$) who had undergone first-time cardiac surgery were sequentially enrolled in the study after obtaining their written informed consent. All the patients underwent cardiac surgery at a regional highly specialized hospital and were admitted for rehabilitation between November 2010 and July 2011. Age greater than 75, an inability to read or understand Italian, visual or auditory impairments, the use of psychotropic drugs, other life-threatening medical illness, and prior cerebrovascular and/or neurological diseases were the exclusion criteria. Seven patients declined to participate because of scheduling for other rehabilitation protocols or unavailability. The remaining patients ($N = 26$) received information on the entire procedure of the study. All patients were also provided with information on pre- and post-training assessments and were informed about the TAU procedures. Then, each patient was randomly assigned to the RSA-biofeedback + TAU group ($N = 13$) or to the TAU group ($N = 13$). All the patients were treated with beta-blocker and/or angiotensin-converting enzyme inhibitor medications.

Psychological Measures

The psychological evaluation included a short clinical interview and three self-report questionnaires aimed at assessing depressive and anxiety symptoms. The depressive and anxiety symptoms questionnaires included:

1. CES-D (Fava 1982; Radloff 1977), which consists of 20 items representing the more common symptoms of depression. The scores range from 0 to 60, with higher scores indicating higher depressive symptoms. Scores greater than 16 are indicative of clinically significant depression. The Cronbach's alpha of CES-D scale in the present study was 0.88.
2. STAI Y1/Y2 (Spielberger et al. 1970, 1996), which comprises two 20-item scales that measure state and trait anxiety, respectively. State anxiety represents the subject's current and transitory anxiety, while trait anxiety indicates a long-lasting and persistent anxiety. The raw scores on each subscale range from 20 to 80, with higher scores reflecting higher levels of anxiety. The Cronbach's alpha of STAI Y1 and Y2 in the present study was 0.92 and 0.84, respectively.

Physiological Recording

Physiological measures were recorded in a standardized fashion using a computerized recording system (ProComp Infiniti, Thought Technology; Montreal, Canada). Blood volume pulse (BVP) was recorded through a photoplethysmographic detection sensor attached to the left ring finger. Because the electrical and mechanical activities of the heart are coupled, photoplethysmography can be used to determine the normal-to-normal (NN) intervals (or inter-beat intervals, IBI), and HR corresponds to the reciprocal of the N-to-N intervals. The HR signal derived from the analog output of the BVP amplifier was processed via a 12-bit analog-to-digital converter with a sampling rate of 256 Hz and stored sequentially for spectral analysis. All the HR data were exported in the Kubios-HRV 2.0 (Kuopio, Finland) software to correct artifacts with a piecewise cubic spline interpolation method that generates missing or corrupted values into the IBI series. Respiration was recorded with two strain gauges/tube filled with conduction fluid worn thoracically and abdominally.

During both the assessment and the training phases, RSA was employed as a reasonable and reliable measure of cardiac vagal tone (Grossman and Taylor 2007). The mechanisms that produce RSA comprehend the interaction between the cardiac and respiratory responses (Grossman 1983), so respiration can confound the relationship between cardiac vagal tone and RSA (Grossman and Taylor 2007; Lehrer et al. 2006). Therefore, the respiration rate range was calculated for each patient (i.e., maximum minus minimum respiration rate, expressed in cycles/min), and converted in Hz (i.e., from cycles/min to cycles/s). Then, a fast Fourier transformation was applied to the variation of IBI occurring within the specific respiration rate range for each patient. Successively, RSA epochs were averaged for each assessment phase (i.e., pre-training and post-training assessments, see below). RSA values were expressed in ms^2 .

Pre-training resting blood pressure was recorded in the left arm using a Tensoval Duo Control (Hartmann; Heidenheim, Deutschland) according to the European Society of Hypertension international protocol (De Greeff et al. 2008). Three readings were taken at intervals of 1 min, and averaged, according to the recommendations for blood pressure measurement of the American Heart Association (Pickering et al. 2005).

Assessment

All patients underwent the same assessment protocol the day after admission for rehabilitation (i.e., pre-training, approximately 10 days after cardiac surgery) and at discharge from the hospital (i.e., post-training, approximately 25 days after cardiac surgery). The assessment protocol

consisted of a psychological evaluation aimed at assessing psychological disorders, particularly symptoms of depression and anxiety. Self-report questionnaires for depressive and anxiety symptoms were administered individually before and after the training by a trained psychologist blind to the patient's group assignment (RSA-biofeedback + TAU or TAU). After the psychological evaluation, blood pressure was measured and HR and respiration were recorded over a 4-min baseline to obtain the basal RSA. All physiological recordings were taken with the patients sitting on a semireclined armchair at a 70° angle after adaptation to the laboratory. No support for the legs was employed in order to avoid possible confounding effect of body position on cardiac activity. The light was dimmed to provide a relaxing atmosphere and the temperature in the room was approximately 21 °C. During the basal physiological recordings, all patients were asked not to close their eyes to avoid differences between groups in the procedure used during the assessment.

Intervention Protocol

Patients were randomized to receive either five sessions of RSA-biofeedback + TAU or the TAU protocol. RSA-biofeedback was designed to increase RSA and, therefore, to counter vagal inhibition associated with depression (Lehrer et al. 2000). The RSA-biofeedback training was scheduled approximately once a day within a 2-week period, and each session lasted about 45 min. The RSA-feedback was presented through a 15-inch monitor connected to a Biograph Infiniti biofeedback machine (Thought Technology; Montreal, Canada). Before starting the first biofeedback training session, patients who underwent RSA-biofeedback intervention were told that learning to increase the size of HR changes in phase with breathing (i.e., RSA) would help them to exercise important responses that regulate the autonomic nervous system. Increased autonomic regulation, in turn, would improve patients' ability to cope with everyday stress (Lehrer et al. 2000). Then, all the patients were informed about the feedback system and about the physiological measures being monitored (i.e., HR and respiration). Further, they were introduced to RSA-biofeedback procedure. After BVP sensor and respiration strain gauge attachment, two six min RSA trainings were performed. Physiological feedback was monitored visually showing a concurrent HR beat-to-beat tachogram (i.e., beats/min) (red line) and abdominal (blue line) breath respiration (i.e., cycles/min). The beat-to-beat tachogram and abdominal respiration were superimposed on the same axes and the on-line moving feedback display was updated at successive 30-s periods. During each RSA-biofeedback training session, patients were instructed to maximize RSA using the

tachogram display (red line) and abdominal respiration (blue line). Specifically, the RSA-biofeedback training goal was to synchronize the HR (red line) with abdominal breathing (blue line). To facilitate HR/breathing synchronization and to maximize RSA amplitude, all the patients were instructed to breathe abdominally at a decreased rate (Del Pozo et al. 2004; Lehrer et al. 2000; Nolan et al. 2005). During each RSA-biofeedback session, all patients were asked not to close their eyes to avoid differences in the procedure used during the assessment and biofeedback training phases. Each patient was reminded not to breathe too deeply to avoid hyperventilation symptoms. No pacing stimulus was provided during each training session. After the completion of each session, patients were also encouraged to regularly practice this exercise for two 15-min periods per day. All RSA-biofeedback sessions were conducted in the same setting used during the pre- and post-training assessment.

Both groups (RSA-biofeedback + TAU or the TAU) received TAU that consisted of daily counseling sessions such as dietary and smoking cessation counseling, weight management, and stress management according to the guidelines of the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation (Balady et al. 2000; Task Force 2003).

Statistical Analysis

Analyses of variance (ANOVAs), with group (RSA-biofeedback + TAU, TAU) as the between-subjects factor, was used to compare the age, education, resting HR, IBI, abdominal and thoracic respiration rates, and blood pressure of the two groups. Fisher's exact test or Chi-square analyses were conducted to compare the two groups in terms of demographic, biomedical, and behavioral variables. Separate mixed analyses of covariance (ANCOVAs) with group (RSA-biofeedback + TAU, TAU) as a between-subjects factor, time (pre-training assessment, post-training assessment) as a within-subjects factor, and age and gender as covariates were conducted on the physiological measures, namely HR, IBI, abdominal and thoracic respiration rates and RSA, as well as on the psychological measures, namely the STAI Y1/Y2, and CES-D scores. Age and gender were entered as covariates a priori because of their influence on RSA (Craft and Schwartz 1995). Kolmogorov–Smirnov-test for normal distribution was performed for each dependent variable, showing that all data were normally distributed ($p > .11$) except for thoracic respiration rate. This latter measure was normalized using logarithmic transformation. Partial eta-squared (η_p^2) was reported as a measure of the effect size. The η_p^2 values considered to represent small, medium, and large effects are .01, .06, and .14, respectively (Cohen 1977).

Fisher's LSD test was used for post hoc analyses. Moreover, hierarchical linear regression analyses were used to predict changes in CES-D, STAI Y1 and Y2 scores from changes in RSA from pre- to post-training periods, while controlling for abdominal respiration rate. Specifically, changes in RSA were entered in Step 1, and then changes in abdominal respiration rate were entered in Step 2. A p value of $<.05$ was considered statistically significant. All statistical analyses were performed using STATISTICA 6.1 (StatSoft Inc., Tulsa, OK, USA).

Results

Characteristics of Patients Who Underwent RSA-Biofeedback Plus TAU and TAU

Fisher's exact test and the Chi-square analysis revealed no group differences for gender ($p = .99$), surgical procedure ($p = .39$), diabetes ($p = .99$), hypertension ($p = .99$), myocardial infarction ($p = .99$), dyslipidemia ($p = .24$), percutaneous transluminal coronary angioplasty (PTCA) ($p = .59$), and smoking ($p = .77$). Similarly, ANOVAs yielded no group differences for age ($F(1, 24) = 0.80$, $p = .38$, $\eta_p^2 = .03$), education ($F(1, 24) = 0.80$, $p = .38$, $\eta_p^2 = .03$), IBI ($F(1, 24) = 0.01$, $p = .91$, $\eta_p^2 = .0005$), HR ($F(1, 24) = 0.32$, $p = .57$, $\eta_p^2 = .01$), abdominal ($F(1, 24) = 1.71$, $p = .20$, $\eta_p^2 = .07$) and log thoracic respiration rates ($F(1, 24) = 3.33$, $p = .08$, $\eta_p^2 = .12$), systolic blood pressure ($F(1, 24) = 1.90$, $p = .18$, $\eta_p^2 = .07$), and diastolic blood pressure ($F(1, 24) = 0.26$, $p = .61$, $\eta_p^2 = .01$). The descriptive statistics for each group are reported in Table 1.

Effects of Biofeedback on Physiological Measures

The group by time ANCOVA on RSA yielded a main effect for the group ($F(1, 22) = 11.26$, $p < .01$, $\eta_p^2 = .34$), and a group \times time interaction effect ($F(1, 22) = 14.6$, $p < .001$, $\eta_p^2 = .40$). This interaction is depicted in Fig. 1. Post hoc Fisher's LSD comparisons showed a significant increase in RSA from pre- to post-training in the RSA-biofeedback + TAU group ($p < .001$), whereas no significant difference in RSA from pre- to post-training was found in the TAU group ($p = .85$). Also, compared to the patients who received TAU, the patients who underwent RSA-biofeedback + TAU had significantly greater RSA in the post-training ($p < .0001$). ANCOVAs did not show any main effect for group and time on IBI (all p 's $> .70$), HR (all p 's $> .61$), abdominal (all p 's $> .12$) and log thoracic respiration rates (all p 's $> .24$). Moreover, no group \times time interaction effects were found for IBI ($F(1, 22) = 0.06$, $p = .81$, $\eta_p^2 = .003$), HR ($F(1, 22) = 0.05$, $p = .82$, $\eta_p^2 = .002$), abdominal ($F(1, 22) = 2.54$, $p = .13$,

Table 1 A comparison of the demographic and biomedical characteristics of the groups

| Variable | RSA-biofeedback +TAU (N = 13) | TAU (N = 13) | p |
|---------------------------------------|-------------------------------|--------------|-----|
| Age (years) | 61.3 (8.1) | 58.3 (9.0) | .38 |
| Education (years) | 10.9 (3.8) | 9.7 (2.7) | .38 |
| Male Gender (N, %) | 11 (85) | 12 (92) | .99 |
| Surgical procedure | | | .39 |
| CABG (N, %) | 4 (31) | 8 (61) | |
| Heart valve (N, %) | 4 (31) | 1 (8) | |
| Combined (N, %) | 5 (38) | 4 (31) | |
| Diabetes (N, %) | 2 (16) | 3 (23) | .99 |
| Hypertension (N, %) | 7 (54) | 8 (61) | .99 |
| Myocardial infarction (N, %) | 1 (8) | 2 (16) | .99 |
| Dyslipidemia (N, %) | 5 (38) | 9 (69) | .24 |
| PTCA | 1 (8) | 3 (23) | .59 |
| Smoking | | | .77 |
| Actual (N, %) | 2 (16) | 3 (23) | |
| Past (N, %) | 3 (23) | 4 (31) | |
| No (N, %) | 8 (61) | 6 (46) | |
| HR (bpm) | 72.7 (10.8) | 75.5 (13.8) | .57 |
| IBI (ms) | 845 (145) | 836 (254) | .91 |
| SBP (mmHg) | 101.3 (7.4) | 105.8 (9.1) | .18 |
| DBP (mmHg) | 65.4 (8.3) | 64.0 (5.2) | .61 |
| Abdominal respiration (cycles/min) | 16.4 (1.8) | 15.0 (3.5) | .20 |
| Log thoracic respiration (cycles/min) | 3.0 (0.0) | 2.9 (0.1) | .08 |

Data are M (SD) of continuous and N (%) of categorical variables
RSA respiratory sinus arrhythmia, TAU treatment as usual, CABG coronary artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, HR heart rate, bpm beats per minute, IBI inter-beat intervals, SBP systolic blood pressure, DBP diastolic blood pressure

$\eta_p^2 = .10$) and log thoracic respiration rates ($F(1, 22) = 1.86$, $p = .19$, $\eta_p^2 = .08$).

Effects of RSA-Biofeedback on Symptoms of Depression and Anxiety

The group by time ANCOVA on CES-D scores yielded a significant group \times time interaction effect ($F(1, 22) = 4.31$, $p < .05$, $\eta_p^2 = .16$). Post hoc Fisher's LSD comparisons showed a significant decrease in CES-D scores from pre-training to post-training in the RSA-biofeedback + TAU group ($p < .02$), whereas no significant difference in the CES-D scores from pre- to post-training was found in the control group ($p = .95$). No significant differences between groups in the pre- ($p = .27$) and post-training periods ($p = .37$) in the CES-D scores were noted.

In the case of STAI Y1, the group by time ANCOVA did not reveal a significant main effect for the group ($F(1,$

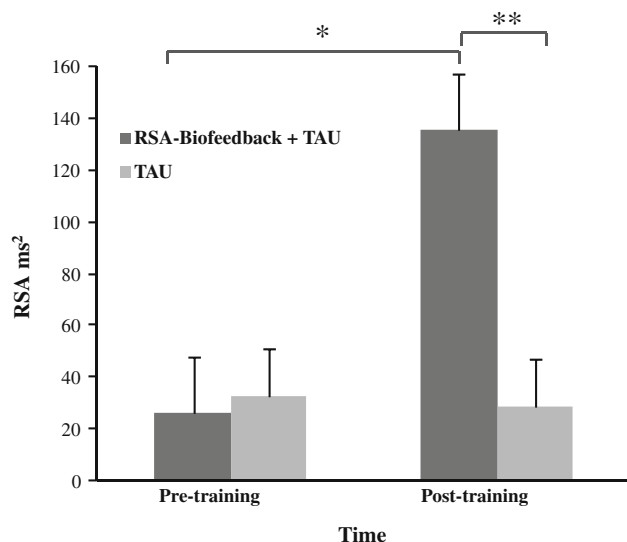


Fig. 1 Pre- and post-training respiratory sinus arrhythmia (RSA) values (ms^2) in RSA-biofeedback group and controls. ANCOVA revealed a significant Group \times Time interaction effect ($p < .001$). Notes: * Post hoc Fisher's LSD comparisons, $p < .001$; ** Post hoc Fisher's LSD comparisons, $p < .0001$; TAU treatment as usual

$22) = 0.55$, $p = .47$, $\eta_p^2 = .02$), time ($F(1, 22) = 1.16$, $p = .29$, $\eta_p^2 = .05$), or group \times time ($F(1, 22) = 1.28$, $p = .27$, $\eta_p^2 = .05$). Similarly, the group by time ANCOVA on the STAI Y2 scores failed to show a significant main effect for the group ($F(1, 22) = 1.22$, $p = .28$, $\eta_p^2 = .05$), time ($F(1, 22) = 0.31$, $p = .58$, $\eta_p^2 = .01$), or group \times time ($F(1, 22) = 2.51$, $p = .13$, $\eta_p^2 = .10$). All means (SD) and statistical details are reported in Table 2.

Relationship Between RSA, CES-D, and STAI Y1/Y2 Scores

Hierarchical linear regression analysis showed that changes in CES-D scores were predicted by changes in RSA from pre- to post-training periods ($\beta = -.50$, $p = .03$). In contrast, changes in RSA were not related to changes in STAI Y1 ($\beta = .15$, $p = .55$), and STAI Y2 ($\beta = .06$, $p = .81$) scores. It is worth noting that changes in abdominal respiration rate did not predict changes in any psychological scores (all p 's $> .26$).

Discussion

The present study investigated the potential effectiveness of RSA-biofeedback training for increasing RSA, as a measure of vagal tone modulation, in patients who had undergone first-time cardiac surgery. It also aimed to elucidate whether an increase in vagal tone would reduce depressive and/or anxiety symptoms. We found that, compared to the patients

Table 2 ANCOVA on depression, state and trait anxiety scores from pre- to post-training in patients who underwent RSA-biofeedback + TAU and TAU

| Variable | Pre-training | Post-training | p | η_p^2 |
|-----------------------|--------------|---------------|--------|------------|
| CES-D | | | $<.05$ | .16 |
| RSA-biofeedback + TAU | 15.3 (11.2) | 8.9 (4.5) | .02 | |
| TAU | 11.8 (6.9) | 11.7 (7.8) | .95 | |
| STAI Y1 | | | .27 | .05 |
| RSA-biofeedback + TAU | 46.0 (8.9) | 42.2 (6.5) | | |
| TAU | 45.2 (7.6) | 43.8 (8.0) | | |
| STAI Y2 | | | .13 | .10 |
| RSA-biofeedback + TAU | 43.9 (6.3) | 43.6 (4.9) | | |
| TAU | 47.6 (7.8) | 43.7 (5.7) | | |

Data are M (SD)

ANCOVA analysis of covariance, RSA respiratory sinus arrhythmia, TAU treatment as usual, CES-D center for epidemiological study depression, STAI Y1/Y2 state and trait anxiety inventory

who received TAU, RSA significantly increased from pre- to post-training in patients who underwent RSA-biofeedback + TAU. Moreover, the patients who underwent RSA-biofeedback + TAU were characterized by a reduction in depressive symptoms from pre- to post-training compared to patients who underwent the standard rehabilitation protocol (i.e., the TAU group). Although our patients did not meet the diagnostic criteria for major and minor depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV, American Psychiatric Association 1994), the patients who underwent RSA-biofeedback + TAU had more depressive symptoms than patients who received TAU in the pre-training period. While the mean (SD) score on CES-D was 11.8 (6.9) in the TAU group, in the RSA-biofeedback + TAU group it was 15.3 (11.2) that falls close to the CES-D cut-off value for mild depressive symptoms (i.e., 16). It is important to note that RSA-biofeedback group showed a significant reduction in the CES-D scores from pre- to post-training ($M = 8.9$, $SD = 4.5$), whereas CES-D scores did not change in the TAU group (post-training, $M = 11.7$, $SD = 7.8$). Consistent with these findings, linear regression analyses showed that changes in RSA were selectively associated with changes in CES-D scores but not in STAI Y1 and Y2 scores from pre- to post-training. Moreover, it is worth noting that this association between changes in RSA and CES-D scores was independent of abdominal respiration rate.

These novel findings add to the literature on the bio-behavioral treatment of cardiovascular disease by showing that the effectiveness of RSA-biofeedback intervention for increasing vagal modulation extends to patients after

cardiac surgery, even under beta-blocker medication. More importantly, our study suggests the effectiveness of RSA-biofeedback in treating depressive symptoms as revealed by the association between changes in RSA and CES-D scores from pre- to post-training. These preliminary findings complement recent studies that have documented RSA-biofeedback effectiveness in enhancing vagal tone (Cowan et al. 1990; Del Pozo et al. 2004; Nolan et al. 2005), as well as for reducing depressive symptoms in patients with coronary heart disease (Nolan et al. 2005). The current results are also in line with previous findings showing the effectiveness of RSA-biofeedback in several clinical populations such as patients with asthma (Lehrer et al. 1997, 2004), chronic obstructive pulmonary disease (Giardino et al. 2004), fibromyalgia (Hassett et al. 2007), or in healthy individuals (Lehrer et al. 2003).

RSA-biofeedback training may add to the efficacy of cognitive behavioral psychotherapy designed to treat depressive symptoms in patients who have undergone first-time cardiac surgery. Indeed, cognitive behavioral interventions are aimed at treating depression by enhancing the cognitive priming of positive emotion, relaxation, and pleasurable social activities as well as by inhibiting cognitive rumination on negative events and negative self-talk. However, the psychophysiological networks and autonomic nervous system pathways that mediate the influence of cognitive behavioral therapy on depression and/or anxiety are still partially unknown. In contrast, our preliminary findings suggest that RSA-biofeedback training may independently enhance HR vagal modulation and reduce depressive symptoms with beneficial effects on postoperative patients' functional and clinical outcome. Although the crucial mechanisms underlying the effectiveness of RSA-biofeedback in enhancing vagal tone modulation are still debated (Wheat and Larkin 2010), it is plausible that RSA-biofeedback may increase peripheral HR modulation by making the baroreceptors more efficient (Lehrer et al. 2000, 2003). However, given that the baroreflex gain was not recorded in the current study, the likelihood of that possibility is indeterminable.

Although not directly investigated in the present study, RSA-biofeedback may reduce postoperative cardiac events by acting on pathophysiological mechanisms underlying the influence of depression on cardiovascular diseases morbidity and/or mortality, especially the altered autonomic nervous system activity (Carney et al. 2000). Additional research is needed to compare the efficacy of RSA-biofeedback and pharmacological therapy with SSRIs in reducing depressive symptoms as well as risk of cardiac mortality and morbidity in patients with cardiovascular diseases and/or in those individuals who underwent cardiac surgery (Berkman et al. 2003; Lespérance et al. 2007).

Another speculative explanation for the current findings may lie in the relationship among RSA-biofeedback, medullary neurons in the cardiorespiratory network, and cortical frontal-limbic circuits (Bennaroch 1997; Thayer and Lane 2000). Given that, during RSA-biofeedback, patients are engaged in maintaining concentration in a targeted physiological index (i.e., RSA), biofeedback may increase vagal tone by evoking concurrently generalized emotional self-control and focused attention. This psychological response may be associated with a brain network that involves the prefrontal and anterior cingulate cortex, which, in turn, are neural substrates of goal-directed behavior and emotion, respectively (Thayer and Lane 2000). The prefrontal and anterior cingulate cortex are, in turn, connected with the amygdala, insula, parabrachial nucleus, lateral hypothalamus, and medullary neurons involved in the parasympathetic and sympathetic modulation of the heart and, therefore, have been linked to neurocardiac regulation (Bennaroch 1997; Thayer and Lane 2000). Interestingly, Kubota et al. (2001) reported that a meditation procedure can increase vagal modulation as well as prefrontal cortex activity. Although there is evidence for an interface between cardiac regulation and cognitive-emotional functioning, future research on the effectiveness of biofeedback training is warranted to examine this potential relationship.

The current findings should be interpreted in light of a number of possible methodological issues. First, this study used a relatively small sample size; therefore, the present results need to be replicated to fully understand the effectiveness of RSA-biofeedback in treating depressive symptoms in patients after cardiac surgery. Nonetheless, the effect size, which indicates the proportion of the variance in the dependent variable that is related to the independent variable(s), showed large group \times time effects on RSA ($\eta_p^2 = .40$) and CES-D scores ($\eta_p^2 = .16$). Second, all the patients were treated in the hospital with a beta-blocker and/or angiotensin-converting enzyme inhibitor medication which, in turn, influenced cardiovascular physiology and, therefore, the blood pressure, HR, and RSA values. However, the pharmacological treatment was a part of these cardiac patients' standard clinical care in this post-surgical context and was the same between the RSA-biofeedback + TAU group and the TAU group. Third, we employed photoplethysmography instead of electrocardiogram, which, in turn, is the gold-standard method to measure HR, HRV, and RSA. Nonetheless, several studies have reported that the parameters of photoplethysmographic variability are highly correlated with HRV and RSA extracted from electrocardiogram (Lu et al. 2008). Fourth, the lack of a non-contingent RSA biofeedback group makes it somewhat difficult to understand whether the results observed in the present study may be fully

attributable to RSA biofeedback intervention. Therefore, future investigations should include a non-contingent RSA feedback group to test more rigorously the efficacy of RSA biofeedback against such a genuine placebo controls. Finally, although the current study showed that RSA is modifiable through biofeedback in an acute timeframe, we did not conduct follow up evaluations, so we do not know whether the current results on RSA and depressive symptoms will be long-lasting (Wheat and Larkin 2010). This latter limitation prevents us from making any definitive conclusions regarding the true effectiveness of RSA-biofeedback for reducing long-term depressive (and anxiety) symptoms in cardiac surgery patients. The questionnaires used in the current study, especially the STAI Y2 that evaluates persistent anxiety, imply ratings that should be performed over an extended period of time. Clearly, future research is warranted to replicate and extend the present findings by conducting long-term follow-up studies to demonstrate the longevity of the improvements in RSA and depressive symptomatology in post-surgical patients. Future studies should also investigate the effectiveness of RSA-biofeedback on trait anxiety over a longer period than 2 weeks.

The current study, to our knowledge, is the first to investigate, in addition to the standard rehabilitation program, the effectiveness of RSA-biofeedback training for increasing vagal modulation as well as for reducing depressive symptoms in patients after cardiac surgery. Our preliminary findings may extend the potential effectiveness of RSA-biofeedback to the post-surgical period and suggest that this novel biobehavioral training may add to the efficacy of postoperative risk reduction programs and cardiac rehabilitation protocols.

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