**ORIGINAL ARTICLE** 



# Acute High-Intensity Exercise Reduces Performance Anxiety: A Pilot Study in Wind Musicians

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## ABSTRACT

**Background.** Musicians' sympathetic arousal needed to deal with an extraordinary event (e.g., a demanding concert) can become a neurophysiological alteration known as Musical Performance Anxiety, an important health problem. **Objectives.** This study aimed to find whether high-intensity interval training (HIIT) might reduce anxiety in musicians after acute training. **Methods.** Ten young wind instrument musicians  $(23.00 \pm 4.88 \text{ years}; 78.86 \pm 11.46 \text{ kg})$  performed two concerts in one week. Forty-eight hours after the first concert, they underwent a magnetic roller training session to get tested and familiarized, and again 48 hours later, they conducted 2-to-4 bouts of 30-second all-out workouts, interspersed with 4 minutes of recovery, between the two concerts. Self-reporting methods (STAI, CSAI-2R) and physiological methods (Heart Rate Variability) were used to test anxiety reduction. **Results.** Pre-post-exercise comparisons revealed a significant reduction (p < 0.05) in both questionnaires. Regarding heart rate variability, Friedman Anova tests revealed also significant differences in Low Frequency (LF; p < 0.05), Low Frequency/High-Frequency ratio (LFHF; p < 0.01), Root Mean Square of successive normal R-R intervals (RMSSD; p = 0.01), Detrended Fluctuation Analysis (DFA1; p < 0.01) and Sample Entropy (SampEn; p < 0.01) after HIIT. **Conclusion.** After the training, the HRV indices' improvement could confirm the hypothesis of parasympathetic reactivation and a better vagal balance as much in the last moment as during the performance. Acute high-intensity exercise may be an efficient solution in the short term for the anxiety problems that musicians suffer in their intense careers.

KEYWORDS: Heart Rate, Mental Health, Psychopathology, Psychophysiology.

## **INTRODUCTION**

The beneficial effects of physical exercise on health are unquestionable in modern medicine (1). More specifically, in psychological health, the influence of physical exercise has been specially investigated in anxiety disorders (2), although it remains unclear the exact mechanism by which physical activity impacts them (2, 3).

Research in this field has been divided into two scopes (4). On the one hand, most studies have examined the effects of regular exercise on trait-anxiety [TA] (a stable susceptibility or a proneness to experience anxiety frequently). On the other hand, different studies have investigated the acute effect of short interventions (1-2 sessions of physical exercise) on state-anxiety [SA] (a transitory emotional state that varies in intensity and fluctuates over time). In this way, some reviews (5, 6) have concluded that TA is reduced when physical exercise is aerobic, with sessions of more than 20 minutes and when the

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training program is maintained for at least ten weeks, referring to the effect of regular physical exercise, while acute interventions of physical exercise on SA show contradictory results (7, 8), with some studies pointing to similar effects to programs of regular exercise (aerobic exercise, low-moderate intensity, sessions of 20-60 minutes) (9-11).

However, the effect of physical exercise on specific phobias, like Music Performance Anxiety (MPA), is less developed. Specifically, only de Figueiredo Rocha, Marocolo (12) have investigated the effect of regular and aerobic exercise on MPA, a kind of social phobia that has been described as "a state of arousal and anxiety occurring before or while a person is performing non-anonymously in front of an audience producing a valuable or evaluated task touching on his/her self-esteem" (13). Some studies confirm high scores on SA and TA (13, 14), as well as in cognitive and somatic anxiety (15) in MPA situations, so MPA may represent a severe problem that musicians have to face during their entire career as performers (16).

Recently, high-intensity interval training (HIIT) has been proposed as a treatment in the field of mental health (17) and mental disease (18). Some authors have shown that HIIT generates greater pleasure than programs of moderate intensities (19), with changes in mood depending on the intensity of the effort (20). However, there is little evidence regarding the benefits of HIIT on specific phobias, and up to our knowledge, no studies have investigated the effect of HIIT on MPA.

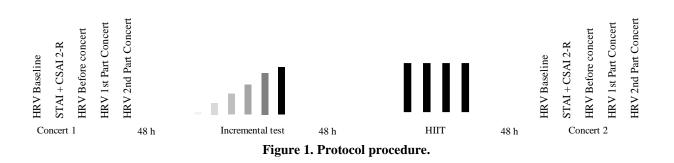
In addition, MPA may be considered a specific state of anxiety associated with the general responses and activation of the organism in situations of pre-competition or performance (21, 22), so it is acceptable that it is related to the autonomic nervous system (ANS) functioning, similar to sports performance anxiety (23). This rationale supports that heart rate variability (HRV) analysis might benefit the control of MPA from a psychophysiological point of view. HRV is mainly modulated by the ANS (24). It is sensitive to changes in the emotional state, and it is already suggested its usage as an analysis technique for identifying the interaction between heart and brain, especially the so-called nonlinear indexes (23, 25, 26), and the control of performance anxiety concerning exercise responses (23, 27).

Therefore, it can be attractive to have deep knowledge of how high-intensity exercise might affect HRV responses and counteract high levels of sympathetic activation in performance anxiety situations (such as a music concert). Thus, this study aims to analyze MPA changes after one week of HIIT in a group of young musicians facing two demanding concerts. Whether the high-intensity approach might reduce the anxiety in wind musicians after acute training must be elucidated. Moreover, we hypothesize that since the mechanisms of HIIT are more intense and cause more remarkable organic changes, these changes may be sufficient to produce acute modifications in the MPA, which both anxiety questionnaires and HRV indexes may reflect.

## **MATERIALS AND METHODS**

Participants. 12 healthy male wind-players recruited from a wind ensemble of the Musical Society of Rafelbuñol (Valencia) participated in this study, approved by the Ethics Committee of the University of Valencia (H143029150232). Inclusion criteria were (a) male gender, (b) playing a wind instrument, (c) studying professional music degree, and (d) playing the same musical role throughout the whole study. Exclusion criteria were: a) a score under 3 in the International Physical Activity Questionnaire (IPAQ) (28), b) have presented events related to cardiovascular problems, and/or c) have blood pressure disorders. All participants completed a voluntary consent to participate in the study and were asked to avoid caffeine, smoking, and other medication during the experiment days. The final sample comprised ten musicians  $(23.00 \pm 4.88)$ years;  $78.86 \pm 11.46$  kg), since two participants were excluded due to technical issues or artifact errors over 3% in the cardiac signal.

**Procedure and measures.** In order to analyze the influence of high-intensity exercise on the control of MPA, the musicians performed two identical evening concerts, separated by seven days. 48h after the first concert, they underwent an incremental cycling test until voluntary exhaustion to get familiarized with high-intensity exercises and medical supervision. Again, 48h later, they conducted 2-to-4 bouts of 30-s cycling all-out Wingate, interspersed with 4 minutes of recovery, to reach maximum autonomic disorganization. They performed the second concert on the seventh day, reproducing the same program and protocol 48h after this all-out experience (Figure 1).



**High-intensity exercise intervention.** All the musicians performed both exercise sessions with the same road cycling bicycle (Scott solace; Scott, Switzerland), fixed to an electro-magnetic brake roller (Tacx flow ergometer, Tacx, Wassenaar, The Netherlands). Individual technical requirements were fitted every time and always by the same expert. Power and pedaling cadence were controlled using the power meter INpower (Rotor Bike Components, Madrid, Spain), and later registered with the Garmin Edge 800 cycle computer.

Incremental test. According to age and baseline Heart Rate (HR), individual Heart Rate Reserve (HRR) (29) ranges were calculated prior to the test, increasing 5% from 70% to 95%. For 2 to 3 minutes, musicians were instructed to pedal freely to find their comfortable self-selected cadence between 60 and 90 rpm. Then, they warmed-up for 5 minutes under their 70% HRR and started a submaximal incremental test where the pedaling cadence was fixed, and the power increases were adjusted progressively to complete one minute of effort in each of the five HRR stages (75% / 80% / 85% / 90% / 95%). It ensured at least one minute close to the maximum exertion (95% HRR) and considerable power output for the HIIT session.

**High-intensity interval training.** The HIIT training included 2 to 4 adapted cycling Wingate (30). Each bout started with 10-s to accelerate to maximal cadence (70%-to-90% of maximum power) referred in incremental test (5-s to get to the 70%, 5-s to get the 85%), and then a sudden increase until 90% to be maintained for 20-s at the maximum pedaling capacity. Musicians were allowed to remain still or do unloaded cycling during the 4 minutes for recovery. This exercise protocol has previously been safe in sedentary adults (30).

Anxiety questionnaires. The State-Trait Anxiety Inventory (STAI; (31) was used to measure anxiety considering the TA: individual and stable differences in responding to stimuli perceived as threatening; as well as the SA: which is referred to as a transitional period characterized by feelings of tension or apprehension; in both cases varying in time and intensity (31), and changes in the autonomic behavior (32). The validated Spanish version of the STAI (33), used in this study, is a 40-items Likert Scale (20 items for each subscale), ranging from 0 (none) to 3 (very much). It scores from 0 to 60 by adding items after an investment of negative scores; the higher the score, the greater the anxiety.

The Spanish version of the Competitive State Anxiety Inventory-2 (CSAI-2) also measured precompetitive anxiety (21). It consists of a 17-items Likert Scale (1 = strongly disagree, 4 = strongly)agree) divided into three subscales: cognitiveanxiety (CA), somatic-anxiety (SomA), and selfconfidence (SeCo). CA assesses the negative perceptions that the participants have about their performance and the consequences of their results. SomA refers to physiological indicators such as muscle tension, increased heart rate, or upset stomach, and sweating. Finally, SeCo is related to the participant's perception of the chance of success in competition. Similarities between musicians and athletes allow it to provide this questionnaire (15).

Autonomic cardiac control measures. Four sampling conditions were defined to analyze psychophysiological changes on the two performing days: One baseline register (bs) in fasting conditions on the morning of the two concerts; one register just before the concert (bC or pre-concert), after 45 minutes for the instruments warm-up; and two registers during the concert, (C1) on the first 5 minutes of the first part of the concert and (C2) the first 5 minutes of the second part. HR and HRV were continuously registered with an HR monitor Polar RS800 (Polar Electro, Kempele, Finland) set to R-R interval mode and an electrode transmitter belt (T61, Polar Electro Kempele, Finland). The conductive gel was applied, as recommended by the manufacturer. During all the recordings, the musicians remained seated for 10 minutes, with eyes closed and in a quiet atmosphere, with no control over breathing patterns (34).

Later on, data were transferred to Polar Pro Trainer 5 software (Kempele, Finland) for further analysis with the Kubios 2.0 software (The **Biomedical Signal and Medical Imaging Analysis** Group, Department of Applied Physics, University of Kuopio, Finland). Based on the visual requirements of the signal, the correction level (medium, low, and very low) was applied to avoid foreign ectopic beats, followed by the "smoothness prior" method, this last to remove the components considered a trend. HRV analyses were then performed on the central 5 minutes segments, looking for the stationarity of the signal (34). The same researcher carried out the whole analysis process to ensure consistency.

The Root-Mean-Square of successive standard R-R intervals (RMSSD) was computed for the time domain of the HRV analysis, while the Low-Frequency (LF), the High-frequency (HF), and the LF/HF ratio indexes were considered for the frequency domain analysis. Regarding the nonlinear indexes, due to the short length of the cardiac segments and based on previous studies (35), we considered the short-term scaling exponent of the Detrended Fluctuation Analysis technique (DFA1) (36) to quantify self-similarity correlations (4–16 beats). Sample entropy (SampEn) (37) was also added to provide a general indication of the predictability of the time series (38).

In summarizing (Figure 1), in the morning of the two days of the concert it was performed the first 10 minutes of HR recording for the baseline HRV analysis. Thirty minutes before the evening concerts, the musicians completed the two anxiety questionnaires (STAI and CSAI-2R) followed by a new 10 minutes HR recording for the Pre-concert HRV (bC). HRV was also recorded during a musical performance, so all the HRV records were performed in a sitting position.

**Other variables.** Biological data were also collected during the process of participants' selection to characterize the sample. Body composition variables like height, weight, and body fat (BF), were evaluated by bioimpedance (Tanita BC-601, Tokyo, Japan; Tallimeter SECA

222); and arterial oxygen saturation (SaO2) was determined with a pulse oximeter attached to the fourth finger of the left hand (WristOx2-3150; Nonin, Plymouth, MN, USA).

Statistical analysis. The Statistical Package for the Social Sciences software (SPSS version 15.0, SPSS Inc., Chicago, USA) was used to analyze and treat the data, and the significance level was set at p < 0.05. After testing for normality (Shapiro-Wilk normality test), pre-post changes in the anxiety questionnaires (TA, SA, CA, SomA, and SeCo) were analyzed with the Student's T-test or Wilcoxon test for related samples. In contrast, Friedman's ANOVA tests, followed by Wilcoxon matched-pairs post-hoc tests were applied for HRV indexes since various sample conditions and data were skewed.

## RESULTS

**Characteristics of participants.** Table 1 presents the description of the sample before HIIT, including some variables of body composition, regular physical activity, and resting data of heart rate variability. These data reflect a group of healthy subjects with slightly elevated body fat and at the limit of overweight. As established in the exclusion criteria, no subject with an IPAQ score below "moderate physical activity" has participated in this work. In addition, 60% declared leading a very active life.

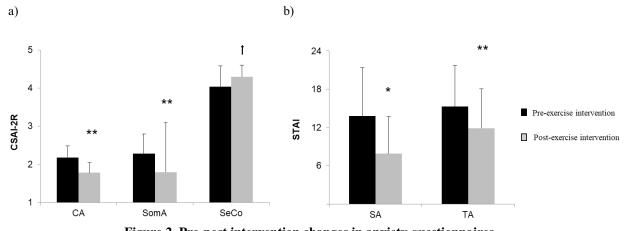
Effects of high-intensity exercise on anxiety questionnaires. Pre-post exercise comparisons revealed a significant reduction in performance anxiety outcomes as SA, TA, CA, and SomA (p < 0.05), and a trend to significance regarding SeCo (p < 0.10), more considerable after training, as shown in Figure 2.

Effects of high-intensity exercise on Autonomic cardiac measures. Regarding the frequency-domain analysis in stationary experimental conditions, bs & bC (Figure 3), the non-parametric Friedman Anova tests revealed significant differences in LF ( $\chi^2 = 16.98$ , N = 10; p < 0.05), LFHF ratio ( $\chi^2 = 33.92$ , N = 10, p < 0.01), and a trend for HF ( $\chi^2 = 13.12$ , N = 10; p = Wilcoxon test pairwise 0.07). Further, comparisons revealed that HF, always higher after the HIIT, was significantly reduced from bs to bC previous to the HIIT intervention (Wilcoxon, Z = -2.30, N = 10, p < 0.05, Cohen's d = 0.69), but not after the exercise (Z = -1.17, N = 10, p = 0.24, Cohen's d = 0.37). This might point to a lower vagal impairment related to performance anxiety after the exercise.

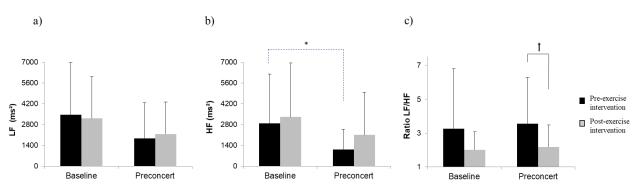
	Ν	Mean ± SD
Age (years)	10	$23.00 \pm 4.88$
Height (m)	10	$1.75\pm0.05$
Weight (kg)	10	$78.86 \pm 11.46$
BMI (kg/m2)	10	$25.55 \pm 3.49$
Body fat (%)	10	$19.23\pm7.45$
SaO2 (%)	10	$97.20 \pm 1.62$
RRi (ms)	10	$941.80 \pm 184.18$
RMSSD (ms)	10	$79.60 \pm 50.32$
LF (ms2)	10	$3444.06 \pm 3523.09$
HF (ms2)	10	$2872.67 \pm 3324.60$
LFHF (ratio)	10	$2.76 \pm 3.56$
DFA1	10	$1.09 \pm 0.32$
SampEn	10	$1.49 \pm 0.27$
IPAQ intensity		
Moderate	4	-
Vigorous	6	-

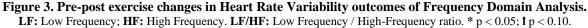
Table 1. Participants' characteristics

**BMI:** Body Mass Index; **SaO2:** arterial oxygen saturation; **RRi:** R-R intervals; **RMSSD:** Root Mean Squares of successive normal R-R intervals; **LF:** Low Frequency; **HF:** High Frequency; **LFHF:** Low Frequency/High-Frequency Ratio; **DFA1:** Detrended Fluctuation Analysis technique (Short terms scaling exponent  $\check{\alpha}1$ ); **SampEn:** Sample Entropy; **IPAQ:** International Physical Activity Questionnaire.



**Figure 2. Pre-post intervention changes in anxiety questionnaires. a)** Results from CSAI-2R. **CA:** cognitive anxiety; **SomA:** Somatic Anxiety; **SeCo:** Self-confidence; **b)** Results from STAI. **SA:** State anxiety; **TA:** Trait anxiety. \*\* p < 0.01; \* p < 0.05; t p < 0.10.





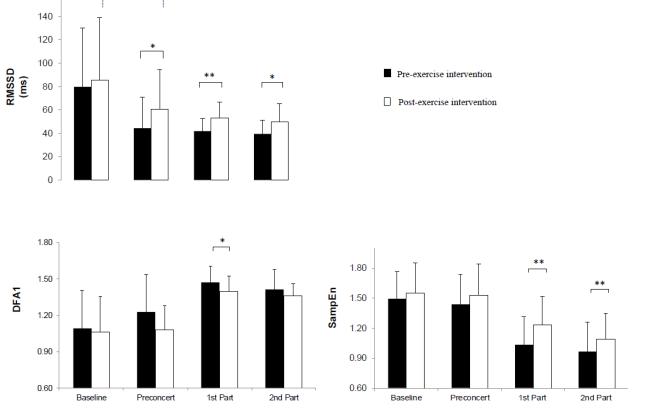
On the other hand, figure 3 also shows that the small changes comparing the pre-post exercise interventions, were positive but not enough to be significant: LF-bs (Z = -0.36, N = 10, p = 0.72,

Cohen's d = 0.07), LF-bC (Z = -0.56, N = 10, p = 0.57, Cohen's d = -0.12), HF-bs (Z = -0.87, N = 10, p = 0.39, Cohen's d = -0.12), HF-bC (Z = -1.38, N = 10, p = 0.17, Cohen's d = -0.44); although the LFHF

ratio, considered a good sympathovagal balance indicator (39, 40), trended to reduce significantly after the HIIT, at least before the concert (Wilcoxon pre-post comparison for LFHF-bC: Z = -1.89, N = 10, p = 0.06, Cohen's d = 1.26; LFHF-bs: Z = -1.48, N = 10, p = 0.14, Cohen's d = 0.45).

**HRV changes in non-stationary situations.** When considering the persistence of anxiety through the concert (Figure 4), which included the non-stationary experimental conditions C1 and C2, Friedman tests revealed significant differences in RMSSD ( $\chi^2 = 18.02$ , N = 10; p = 0.01), DFA1 ( $\chi^2 = 37.71$ , N = 10; p < 0.01) and SampEn ( $\chi^2 = 54.24$ , N = 10, p < 0.01). More specifically, the Wilcoxon post hoc tests showed again that significant withinday changes (bs vs bC) in the vagal indicator RMSSD, better in the RMSSD-bs than RMSSD-bC previous to the exercise sessions (Z = -2.39, N = 10, p < 0.05, Cohen's d = 0.88), that trended to

significance post-exercise (Z = -1.89, N = 10, p < -100.05, Cohen's d = 0.55). These within-day differences were not reflected by DFA1 or by SampEn. On the other hand, attending to the prepost exercise differences (Figure 4), there was always an increase in RMSSD which was significant at RMSSD-bc (Z = -2.19, N = 10, p < 0.05, Cohen's d = -0.52), RMSSD-C1 (Z = -2.80, N = 10, p < 0.02, Cohen's d = -0.89), and RMSSD-C2 (Z = -2.19, N = 10, p < 0.05, Cohen's d = -0.74) but not at RMSSD-bs (Z = -0.66, N = 10, p = 0.51, Cohen's d = -0.11). DFA1 was always lower but it got reduced significantly only at C1 (Z = -2.29, N = 10, p < 0.05, Cohen's d = 0.58); and SampEn increased always too, but it reflected significant differences now at C1 (SampEn-C1: Z = -2.80, N = 10, p < 0.02, Cohen's d = -0.69), and C2 (SampEn-C2: Z = -2.55, N = 10, p < 0.02, Cohen's d = -0.45).



**Figure 4. Pre-post intervention changes in Heart Rate Variability. RMSSD:** Root Mean Squares Standard Deviations, **DFA1:** Detrended Fluctuation Analysis, **SampEn:** Sample Entropy. \*\* p < 0.01; \* p < 0.05;  $\beta p < 0.10$ .

## DISCUSSION

This study supports the use of HIIT prescriptions for the treatment of MPA. A protocol consisting of 2 sessions of high-intensity exercise yielded remarkable reductions in MPA in both psychological (STAI, CSAI-2R) and psychophysiological measures (HRV). This work would be the first to use an acute HIIT intervention in this anxiety disorder.

Regarding HRV outcomes, our results show a decrease in the RMSSD in stress situations; however, this decrease has been significantly lower after exercise in the pre-performance and during the interpretation condition. The RMSSD is an indirect measurement variable of Respiratory Sinus Arrhythmia, so reducing the RMSDD values may indicate a lower tonic-vagal modulation of the heart rate and a lower central respiratory impulse, fewer deep breaths, or a higher respiratory rate. In this way, improved RMSSD values after the intervention could allow the musicians (wind players) to play more comfortably and face more demanding tasks from a respiratory point of view (41, 42). These results differ from Schubert and Lambertz (43), who did not find significant differences in the RMSSD in moments of mental stress like a speech task. Nevertheless, speech task does not demand an intense respiratory change as playing music.

Regarding the results obtained in the complexity variable (SampEn), our data show significant differences in the interpretive moments but not before the concert or in basal moments. In the same line, Anishchenko, and Igosheva (44) showed that this variable decreased significantly during stress (university exams). The decrease in the value of complexity measures reflects a change towards a more stable and periodic heart rate behavior under stress that may be associated with greater regularity in the signal. This reduction in the complexity of HR during a high-stress condition may reflect a lesser ability to adapt to the situation (43). We observe a decrease in entropy in the first part of the first concert, which does not occur in the second concert. Therefore, it is possible that after highintensity exercise, there was a better adaptation of the musicians regarding the demands of the situation in the second concert. Recent studies have started to recommend this modality of exercise (45), at least in clinical populations (46).

Moreover, we have analyzed changes in the fractal analysis of the cardiac signal (DFA1), which offers a deeper insight into cardiac autonomic functioning. We saw a significant alteration in fractality during the concert and a trend to significance in the last moments before the concert, with lower values after HIIT. It would indicate a greater self-similarity of the cardiac signal in the first concert, which implies a lower cardiac variability before the treatment application. These results coincide with Mateo and Blasco-Lafarga's (23) findings.

From our point of view, the general results obtained in HRV reflect a cardiac parasympathetic reactivation after the HIIT session. Some studies that this parasympathetic have suggested reactivation occurs between 24 and 72 hours after exercise (47, 48) and is parallel to the acuteintermediate recovery of the vascular and thermoregulation systems described by the theory of supercompensation (48). Our data could coincide with a more significant role of parasympathetic activity in the moments of stress before the concert. which would counteract the effects of sympathetic activity. Therefore, we want to point out that performing high-intensity exercise is essential for dealing with performance anxiety and planning the appropriate recovery duration to produce parasympathetic reactivation. In this same way, some authors have suggested that improvements in HRV could be an essential resource in coping with emotions because it helps with a flexible adaptation to changing environmental pressures (49). Low HRV resting levels are associated with poor psychological health and are reflected in various mood and anxiety disorders, while high HRV and high HRV resting levels are associated with contextappropriate and regulated emotional responses (50).

Based on the assumption that cardiac autonomic modulation reflects psychophysiological health, HRV would help monitor physiological stress and help musicians prepare the highly demanding music.

Analyzing results from self-report measures shows the positive effect of acute high-intense exercise on TA, SA, CA, SomA, and SeCo. Many works have assessed the effect of high-intensity exercise on anxiety. For example, aligned with our results, Farrell and Gustafson (51) found improvements after exercise, but their training sessions lasted between 40 minutes and 80 minutes. with intensities never above the anaerobic threshold (60-80% VO2max). Other studies collected in the Tuson review (11) show similar results where neither of these works exceeds 90% of the heart rate in their interventions. However, our results differ from those obtained by Martínez-Díaz and Carrasco (52), who obtained no changes in anxiety after a protocol of HIIT. Along the same line, Steptoe and Cox found worse anxiety levels at higher exercise intensities (53). These differences could be due to the moment of the questionnaires; thus, the immediate supply of these questionnaires after exercise would increase anxiety (due to higher levels of sympathetic activation or parasympathetic inhibition). Conversely, making them coincide with the parasympathetic reactivation should reflect increased vagal balance and a decrease in anxiety levels. Therefore, less parasympathetic inhibition would produce a feeling of less anxiety.

Although the current study has several strengths, it is not without limitations. The previous level of physical fitness of the research participants could affect the results of this research. Moreover, the small sample size implicates some uncertainty when extrapolating the results and becomes a limitation to our study. Linked with this, obtaining access to large and specific enough samples is a common difficulty found by researchers in the study of MPA. Thereby, much research on specific phobias is conducted on music students (like in our study), and in consequence, their experience of anxiety may be different from professionals. Future studies should include a greater sample size to better elucidate the mechanisms of high intense exercise on MPA about HRV. Besides, this study has two significant limitations. Firstly, we did not include a control group who did not exercise. It was intentional from an ethical point of view because we considered the evidence of physical exercise's impact on mental health. Secondly, a counterbalance of the concerts could have provided more information about the fundamental role of exercise in this disorder, but due to the small sample size, we did not want to risk losing some participants during the intervention. Finally, HRV, exercise performance, and music performance could be influenced by other variables such as sleep quality or reaction time (54, 55), so future studies should consider and control these factors (among others). We encourage future studies to investigate our same hypothesis with a more robust research design.

# CONCLUSIONS

In conclusion, high intense exercise improved MPA regarding HRV and anxiety questionnaires.

More specifically, improvements in MPA could be due to parasympathetic reactivation after two sessions per week of high-intensity exercise. Consequently, future studies must delve into the impact of highly intense exercise on this type of anxiety.

# APPLICABLE REMARKS

- This study confirms the vital role of exercise in mental health.
- High-intensity training could be a new method to reduce cognitive and physiological symptoms of anxiety in musicians.
- Sports scientists should be deep in this new field of work, helping professional musicians to increase their physical and mental health.

## **AUTHORS' CONTRIBUTIONS**

Study concept and design: P. Monteagudo & C. Blasco-Lafarga. Acquisition of data: P. Monteagudo, A. Cordellat. A. Roldán & C. Blasco-Lafarga. Analysis and interpretation of data: P. Monteagudo & C. Blasco-Lafarga. Drafting the manuscript: P. Monteagudo, A. Cordellat. A. Roldán & C. Blasco-Lafarga. Critical revision of the manuscript for important intellectual content: P. Monteagudo & C. Blasco-Lafarga. Statistical analysis: P. Monteagudo & C. Blasco-Lafarga. Administrative, technical, and material support: A. Cordellat & A. Roldán. Study supervision: C. Blasco-Lafarga.

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## **CONFLICTS OF INTEREST**

The authors have no conflict of interest to declare.

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