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Cardiac autonomic regulation during submaximal exercise in women with fibromyalgia

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Fibromyalgia (FM) patients present impaired cardiac autonomic regulation during maximal exercise; however, it is unknown whether these alterations also manifest during submaximal exercise. The aim of this study was to compare the on-transient heart rate (HR) response and HR variability during a constant-load submaximal cycling exercise between FM and control (CON) women. Ten women with FM (age: 45.2 ± 9.3 years) and 10 age-matched CON women (age: 48.4 ± 6.1 years) performed a 15-min cycling exercise, with the work rate fixed at 50% of the individual peak power output attained in a maximal graded exercise test. The time intervals between consecutive heartbeats were recorded regularly during the exercise for subsequent analysis of on-transient HR response and HR variability indices. The on-transient HR time constant was similar ($P = 0.83$) between the FM (41.0 ± 14.1 sec) and CON (42.2 ± 10.4 sec). During the 5–10 and 10–15 min of exercise, HR variability indices indicating sympathetic and parasympathetic activities were similar ($P > 0.05$) between FM and CON groups. In conclusion, women with FM presented a normal cardiac autonomic response to submaximal cycling exercise. These findings have clinical relevance, as submaximal exercises are commonly prescribed for FM patients.

Keywords: Autonomic function, Chronic widespread pain, Heart rate, Heart rate variability, Steady-state

INTRODUCTION

Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, sleep disturbances, anxiety and depressive episodes, fatigue, and functional limitations (Häuser et al., 2015). Dysfunction in the sympathetic and parasympathetic components of the autonomic nervous system has also been proposed to underlie FM pathophysiology (Meeus et al., 2013; Sarzi-Puttini et al., 2020). Specifically, FM patients reach lower maximal heart rate (HR) during a maximal exercise, caused by impairments in the sympathetic activation and/or parasympathetic withdrawal (da Cunha Ribeiro et al., 2011; Lehto et al., 2023; Maia et al., 2016; Schamne et al., 2021). It is unknown whether these alterations also manifest during submaximal exercise. This is important because, differently from maximal exercise, submaximal exercise is a type of exercise that is commonly used in exercise training programs for the management of FM symptoms (Mannerkorpi and Iversen, 2003). Thus, the identification of possible deficits in cardiac autonomic function during submaximal exercise would be useful for more accurate and safety exercise prescription to this population.

The autonomic nervous system mediates the cardiovascular adjustments necessary to meet the metabolic demands imposed by working skeletal muscle during exercise (Fisher, 2014). During the first minutes of a submaximal exercise (~50% of the individual peak power output, PPO), the combination of parasympathetic withdrawal and sympathetic activation triggers an exponential increase in the HR until the attainment of a steady state (Javorka et al., 2003). A fast on-transient HR response allows adequate blood supply for working muscles (Almas et al., 2017). Potential impairments in the parasympathetic withdrawal and/or sympathetic

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activation might therefore delay the HR on-transient response. Studies investigating the on-transient HR response during constant-load submaximal exercise in FM patients are, therefore, necessary.

While a slow on-transient HR response indicates potential impairments in parasympathetic withdrawal and/or sympathetic activation at the beginning of exercise (Javorka et al., 2003), the balance of sympathetic and parasympathetic activities can also be assessed in the steady-state phase of submaximal exercise by monitoring HR variability (HRV) (Shaffer and Ginsberg, 2017). HRV is a measure of the oscillation that occurs in the time interval between consecutive heart beats (Shaffer and Ginsberg, 2017), and mathematical indices derived from HRV recording are posteriorly calculated to determine the sympathetic and parasympathetic activities (Johnston et al., 2020). Hence, these HRV indices can indicate altered sympathetic and/or parasympathetic nervous system activities under a given perturbation. For example, FM patients did not exhibit a reduction in the SDNN index (i.e., standard deviation of R-R intervals, RRi) of HRV when moving from a supine to standing position, indicating an impaired parasympathetic withdrawal with orthostatic changes (Cohen et al., 2001). However, to our knowledge, no studies have yet measured HRV during a submaximal exercise in FM patients; thus, it remains still unknown whether sympathetic and parasympathetic responses are altered during submaximal exercise in FM patients.

The aim of this study was to compare the on-transient HR and HRV responses during a constant-load submaximal cycling exercise between women with a diagnosis of FM and apparently healthy age-matched women (CON). We hypothesized that FM patients would present delayed on-transient HR response and alterations in HRV indices, indicating imbalance in sympathetic and parasympathetic activities, when compared to their counterparts in the CON group.

MATERIALS AND METHODS

Participants

A statistical power analysis was performed using G*power 3.1 software (Kiel University, Kiel, Germany) to estimate the necessary sample size. As no previous studies have compared the on-transient HR response between FM and CON, data from previous cross-sectional studies comparing the on-transient HR response during exercise between patients with diseases associated with cardiac autonomic dysfunction (e.g., type 2 diabetes) and CON participants were used for the sample size calculation. These studies reported Cohen *d* effect sizes ranging from 0.82 to 3.66 for the effect of autonomic dysfunction on the time constant (τ) of the on-transient HR response (Almas et al., 2017; Regensteiner et al., 1998; Silva et al., 2017). Considering the smallest effect size of 0.82 (Almas et al., 2017), the required number of participants to achieve a power of 0.95 and an alpha of 0.05 was estimated to be nine in each group. Thus, 10 women with a clinical diagnosis of FM according to the American College of Rheumatology criteria (Wolfe et al., 1990; Wolfe et al., 2010) and 10 age-matched apparently healthy CON women participated in this study. The exclusion criteria adopted for both groups were: (a) any cardiovascular abnormalities (arrhythmias and heart failure), (b) articular or bone injury, (c) tobacco usage, (d) use of chronotropic and antihypertensive drugs that could affect autonomic modulation, and (e) pregnancy. The FM patients were taking antidepressant (60%), analgesic (50%), anticonvulsant (40%), anti-inflammatory (10%), and muscle relaxant (10%) drugs. Participants signed an informed consent statement previously approved by the local ethics committee (number protocol approved 5.091.561). This study followed the recommendations established in the Declaration of Helsinki.

Procedures

Data collection occurred on three nonconsecutive days, with an interval of at least 72 hr between days. On the first day, participants underwent anthropometric measurements and performed a maximal graded exercise test on an electromagnetically braked cycle ergometer to determine their PPO. On the second day, participants performed a familiarization session with the 15-min constant-load cycling exercise (50% of PPO). On the final day, participants repeated the 15-min constant-load cycling exercise (50% of PPO) with measurements of HR and HRV indices. The exercise intensity was fixed at 50% of PPO as this corresponds to moderate intensity for women with FM and is commonly used in training programs for FM patients (Hsieh et al., 2010; Lund et al., 2003). Participants were instructed to refrain from vigorous physical activity during the study period and not to ingest alcohol or caffeinated beverages during the 24 hr before the trials. In addition, the FM patients were instructed to maintain their medication intake routine during the study period.

Maximal graded exercise test

Participants started the maximal graded exercise test cycling at 15 W for 1 min; thereafter, work rate was increased by 15 W every minute until exhaustion. Participants were instructed to maintain the pedal cadence between 50 and 60 revolutions per minute

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throughout the test (Schamne et al., 2021; Smeets and Soest, 2009). Exhaustion was defined when participants voluntarily disengaged from the task, or when they were unable to maintain pedal cadence above 50 revolutions per minute for longer than 5 sec, even with verbal encouragement. The rating of perceived exertion (RPE) was measured at the end of each stage using a 15-point Borg scale (Borg, 1982), and the RPE reported in the final stage of the test was defined as peak RPE. The HR was monitored throughout the test using a portable cardiac monitor. The highest HR value recorded during the test was defined as peak HR. The maximum predicted HR was calculated using the equation 208–0.7×age (Tanaka et al., 2001). The PPO was considered as the maximal workload reached during the last completed stage. When the last stage was incomplete, the PPO was calculated using the fraction of the time performed in the last incomplete stage multiplied by the increment rate (Kuipers et al., 2003).

Constant-load submaximal exercise

Participants performed a 3-min warm-up at 15 W, followed by 15 min of cycling at 50% of PPO. They were instructed to maintain the pedal cadence between 50 and 60 revolutions per minute throughout the exercise. The time interval between heartbeats was continuously recorded throughout the exercise using a portable cardiac monitor for subsequent analysis of on-transient HR response and HRV indices.

On-transient HR response

For the assessment of the on-transient HR response, the RRi was transformed into its reciprocal HR (i.e., HR=60/RRi) (D'Agosto et al., 2014). The ectopic heart beats were visually detected and excluded. Individual beat-by-beat HR responses during the exercise were smoothed using the 5-beat moving average (Buekers et al., 2023) and 1-sec interpolated; thereafter, the first 5 min of the HR curve during exercise were fitted by a first-order exponential function using the nonlinear least squares method (Javorka et al., 2003) (Equation 1):

$$HR_{(t)} = HR_0 + A_{on}\{1 - \exp[-(t/\tau)]\} \text{ (Equation 1)}$$

where $HR_{(t)}$ is the HR response, HR_0 is the HR average of the last 30 sec before the beginning of exercise (i.e., baseline HR value), A_{on} is the amplitude of the HR response, t is time, and τ is the time constant (i.e., time to reach 63% of the final HR) (Fig. 1). The goodness of fit was measured by the standard error of estimate (SEE) and the coefficient of determination (R^2).

HR and HR variability

The RRi records of the last 10 min of exercise were used for analysis of mean HR and HRV. The absolute mean HR was calculated in two different 5-min time windows (i.e., 5–10 and 10–15 min of exercise). The mean HR of the 10–15 min interval was also reported as relative to peak HR and maximum predicted HR to determine the relative internal training load (Impellizzeri et al., 2019). The HRV indices were calculated during the 5–10 and 10–15 min of exercise using Kubios HRV Standard software (ver. 3.5.0; University of Eastern Finland, Kuopio, Finland). Initially, the ectopic beats were visually detected and manually excluded. The RRi data were then detrended with the smoothness priors method (k=500) (Tarvainen et al., 2002). The HRV indices were

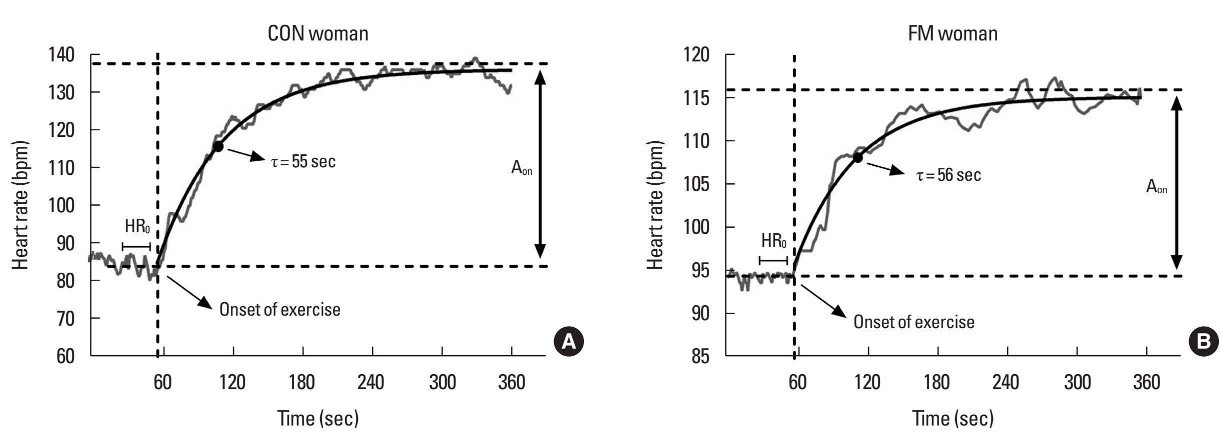

Fig. 1. On-transient heart rate response of representative women from the control (A) and fibromyalgia (B) groups. The grey continuous line is the actual heart rate curve, while the black continuous line is the fitted first-order exponential function. The black dot represents the time constant (τ), which is the time to attain 63% of the final heart rate. The HR_0 is the heart rate before the beginning of exercise and A_{on} is the amplitude of heart rate response. CON, control; FM, fibromyalgia; HR_0, heart rate before the beginning of exercise; A_{on}, amplitude.

Table 1. Participants' characteristics

Characteristic	CON (n=10)	FM (n=10)	*P*-value
Age (yr)	48.4±6.1	45.2±9.3	0.375
Height (cm)	160.2±8.7	162.4±9.6	0.598
Body mass (kg)	64.9±7.5	71.7±14.4	0.200
Body mass index (kg/m²)	25.5±3.9	27.0±4.5	0.421
Disease duration (yr)	NA	11.0±7.0	NA
Peak power output (W)	141.9±14.7	128.9±23.7	0.159
Peak RPE	19.4±0.5	19.4±1.0	0.999
Peak HR (bpm)	160.0±13.0	147.0±16.0	0.055
Peak HR (% of maximum predicted HR)	92.0±6.0	83.0±7.0	0.009

Values are presented as mean±standard deviation.
CON, control women; FM, women with fibromyalgia; NA, not applicable; RPE, rating of perceived exertion; HR, heart rate.

Table 2. Parameters of on-transient heart rate response during a constant-load submaximal exercise in the CON and FM groups

Variable	CON (n=10)	FM (n=10)	*P*-value
τ (sec)	42.2±10.4	41.0±14.1	0.832
SEE τ (sec)	1.1±0.3	1.0±0.5	0.652
SEE τ (%)	2.7±0.9	2.4±0.6	0.413
A_{on} (bpm)	36.0±11.0	30.0±7.0	0.195
SEE A_{on} (bpm)	0.2±0.1	0.1±0.1	0.079
SEE A_{on} (%)	0.5±0.2	0.5±0.2	0.513
HR_0 (bpm)	76.0±10.0	79.0±14.0	0.652
R^2	0.90±0.05	0.90±0.05	0.439

Values are presented as mean±standard deviation.
CON, control women; FM, women with fibromyalgia; τ, time constant; SEE, standard error of estimate; A_{on}, amplitude; HR_0, heart rate before the beginning of exercise; R^2, coefficient of determination.

calculated using linear and nonlinear methods. The HRV indices calculated using linear methods were: (a) standard deviation of consecutive RRi (SDNN), and (b) root mean square of the successive differences between adjacent RRi (RMSSD). The SDNN and RMSSD represented parasympathetic activity (Shaffer and Ginsberg, 2017). The HRV indices calculated with the nonlinear method were obtained via Poincaré plot analysis: (a) standard deviation of the instantaneous beat-to-beat RRi variability (SD_1), (b) standard deviation of the continuous long-term RRi variability (SD_2), and (c) the SD_1/SD_2 ratio. The SD_1 was used to represent the parasympathetic modulation on sinus node, and the SD_2 to represent both parasympathetic and sympathetic components (Shaffer and Ginsberg, 2017). The SD_1/SD_2 ratio was used to represent sympathetic and parasympathetic balance (Shaffer and Ginsberg, 2017).

Statistical analyses

The Gaussian distribution was verified using the Shapiro–Wilk test. The main anthropometric characteristics, PPO, absolute and relative peak HR, parameters of on-transient HR response (τ, A_{on}, HR_0, SEE, and R^2), and absolute and relative mean HR were all compared between FM and CON groups using the Student *t*-test. The homogeneity of variances was confirmed via Levene test. The mean HR and HRV indices were compared using two-way analysis of variance (group: CON and FM vs. time: 5–10 and 10–15 min). The SDNN, RMSSD, SD_1, and SD_2 indices were logarithmically (Ln) transformed to meet the assumptions of parametric testing (i.e., Ln-SDNN, Ln-RMSSD, Ln-SD_1, Ln-SD_2, respectively). The sphericity of the variances was confirmed via Mauchly's test. The significance was accepted when $P \leq 0.05$. All analyses were performed using Jamovi free software (ver. 2.3).

RESULTS

The FM and CON groups were similar in relation to age, anthropometric characteristics, and PPO (all $P > 0.05$). However, the FM patients had lower absolute and relative peak HR than the CON women during the maximal graded exercise test (Table 1).

The parameters of the on-transient HR response are shown in Table 2. There was no difference between FM and CON groups for τ, A_{on}, and HR_0 (all $P > 0.05$). In addition, the SEE values for τ and A_{on}, expressed in absolute and relative values, were similar between the FM and CON groups ($P > 0.05$). The R^2 of the fitted function was also similar between the FM and CON groups ($P > 0.05$).

The mean HR and the HRV indices are shown in Fig. 2. There were no main effects of group and time, or group versus time interactions for mean HR, Ln-SDNN, Ln-RMSSD, Ln-SD_1, Ln-SD_2, and SD_1/SD_2 (all $P > 0.05$). In addition, there was no difference between FM and CON groups for mean HR relative to peak HR (FM: 78%±9% vs. CON: 73%±7%, $P = 0.19$) or relative to maximum predicted HR (FM: 65%±8% vs. CON: 68%±8%, $P = 0.53$).

DISCUSSION

In the present study, we compared the on-transient HR response and HRV indices during exercise between women with FM and CON women. The findings of the present study indicate similar on-transient HR response and HRV indices during the constant-load submaximal exercise between the FM and CON groups, suggesting that FM patients do not present impaired sympathetic

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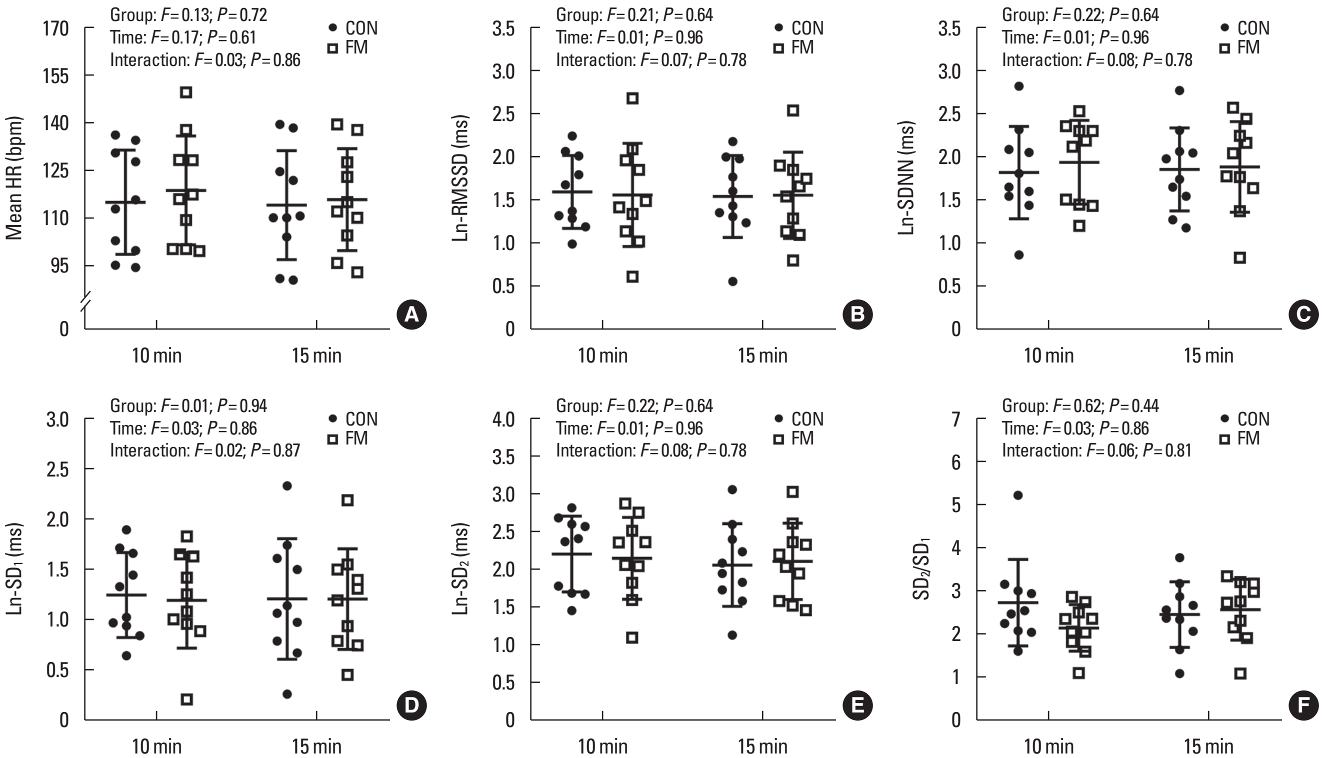

Fig. 2. Mean, standard deviation, and individual data of mean heart rate (HR) and HR variability indices for the 5–10- and 10–15-min time windows of the constant-load submaximal exercise in the control (CON) and fibromyalgia (FM) groups. (A) Mean HR. (B) Ln-RMSSD. (C) Ln-SDNN. (D) Ln-SD_1. (E) Ln-SD_2. (F) SD_2/SD_1. Ln-SDNN, natural logarithm of standard deviation of R-R intervals; Ln-RMSSD, natural logarithm of root mean square of the successive differences between adjacent R-R intervals; Ln-SD_1, natural logarithm of standard deviation of the instantaneous beat-to-beat R-R intervals variability; Ln-SD_2, natural logarithm of standard deviation of the continuous long-term R-R intervals variability.

and parasympathetic activities during this type of exercise.

The similar responses of cardiac autonomic parameters (on-transient HR, mean HR, and HRV indices) between the FM and CON groups is contrary to our hypothesis that FM patients would present impaired cardiac autonomic activity during exercise. In fact, it has been demonstrated that FM patients present impaired sympathetic activation and reduced parasympathetic withdrawal under different conditions of physiological stress, such as orthostatic alterations (Cohen et al., 2001; Contreras-Merino et al., 2022; Furlan et al., 2005), cold immersion (Reyes del Paso et al., 2011), and cognitive stress (Zetterman et al., 2023). While it is difficult to explain why cardiac autonomic reactivity during submaximal exercise is not compromised in FM patients, it could be hypothesized that autonomic reactivity to exercise might become impaired in FM only above a certain level of exercise intensity. Previous studies reported lower peak HR during a maximal incremental exercise in women with FM, indicating impairment in sympathetic activation and/or parasympathetic withdrawal (da Cunha Ribeiro et al., 2011; Lehto et al., 2023; Maia et al., 2016; Schamne et al., 2021). However, for complete sympathetic activation during exercise, great release of adrenaline and noradrenaline from adrenal gland to the plasma is mandatory. Nevertheless, plasma adrenaline and noradrenaline levels increase abruptly only at exercise intensities above individual anaerobic threshold (Urhausen et al., 1994), which in FM women is found at ~64% of PPO (Bardal et al., 2013). Exercise intensities below individual anaerobic threshold are therefore characterized by low metabolic perturbation, resulting in low sympathetic activation (Fisher, 2014). Thus, it is likely that a submaximal cycling exercise (50% of PPO) might not have been sufficiently stressful to provoke a great physiological disturbance, which otherwise could compromise autonomic nervous system reactivity, mainly the sympathetic component. Supporting this assumption, while the mean HR values during the constant-load submaximal exercise were similar between the FM and CON groups, the women with FM attained a lower peak HR and a lower percentage of maximum predicted HR during the maximal graded exercise test than CON women. This lower peak HR in women with FM than in CON women reinforces the lower chronotropic response of FM patients at higher exercise intensities. Our findings suggest therefore that cardiac autonomic responsiveness to submaximal exercise seems to be preserved in FM patients, and failure in parasympathetic withdrawal and/or sympathetic activation manifests in FM patients only when the exercise is of higher intensity.

The results obtained in the present study are relevant to exercise prescription for FM patients. FM patients normally present exacerbation of FM-associated symptoms when practicing exercise (Russell et al., 2018). However, a few weeks of submaximal exercise training have been shown to significantly increase the quality of life and functional capacity and to reduce most of the FM symptoms, such as perceived pain, fatigue, and stiffness (Andrade et al., 2020). Thus, an accurate determination of the exercise intensity is essential to guarantee that the effort is submaximal and therefore to optimize exercise-induced reduction in FM symptoms (Busch et al., 2007). In this context, cardiac autonomic responses are considered representative markers of individual internal training load (i.e., the acute individual response to the prescribed exercise) and can be used to guide exercise prescription (Impellizzeri et al., 2019; Manser et al., 2021). While the similar cardiac autonomic responses to exercise observed between the FM and CON indicate that submaximal cycling exercise provokes a similar internal training load in women with FM and CON women, monitoring HR and HRV indices during exercise could enable adjustment in the exercise intensity according to the physiological specificities and health status of FM patients. Therefore, better knowledge of the cardiac autonomic responses during submaximal exercise in FM patients surely assist a better-oriented exercise prescription for this population.

The present study presents some limitations that should be acknowledged. First, the on-transient HR and HRV responses are indirect measures of cardiac autonomic control (Maqsood et al., 2023; Zakynthinaki, 2015). This method of cardiac autonomic function assessment is widely used as it is noninvasive, low-cost, and relatively easy to implement in research settings as well as in daily clinical practice (Mazzeo et al., 2011; Zakynthinaki, 2015). However, further studies using direct measures of autonomic function (e.g., microneurography) could provide broader understanding of the autonomic response during submaximal exercise in FM patients. Second, the lack of men in the sample precludes conclusions as to whether the autonomic response to cycling submaximal exercise is also preserved in men with FM. Although FM manifests primarily in women (Sarzi-Puttini et al., 2020), further studies are needed that test the cardiac autonomic responses during exercise in men with FM. Even with these potential limitations, the present findings improve the current knowledge of the cardiac autonomic response during submaximal exercise in FM patients.

In conclusion, women with FM do not present abnormal on-transient HR and HRV responses during submaximal exercise, indicating preserved cardiac autonomic function during this type of exercise. These findings have clinical relevance, as submaximal exercises are commonly applied in training programs for FM patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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