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Review

Exercise training-induced modification in autonomic nervous system: An update for cardiac patients

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ABSTRACT

Patients with cardiovascular disease show autonomic dysfunction, including sympathetic activation and vagal withdrawal, which leads to fatal events. This review aims to place sympathovagal balance as an essential element to be considered in management for cardiovascular disease patients who benefit from a cardiac rehabilitation program. Many studies showed that exercise training, as non-pharmacologic treatment, plays an important role in enhancing sympathovagal balance and could normalize levels of markers of sympathetic flow measured by microneurography, heart rate variability or plasma catecholamine levels. This alteration positively affects prognosis with cardiovascular disease. In general, cardiac rehabilitation programs include moderate-intensity and continuous aerobic exercise. Other forms of activities such as high-intensity interval training, breathing exercises, relaxation and transcutaneous electrical stimulation can improve sympathovagal balance and should be implemented in cardiac rehabilitation programs. Currently, the exercise training programs in cardiac rehabilitation are individualized to optimize health outcomes. The sports science concept of the heart rate variability (HRV)-vagal index used to manage exercise sessions (for a goal of performance) could be implemented in cardiac rehabilitation to improve cardiovascular fitness and autonomic nervous system function.

1. Introduction

According to recent epidemiological studies, cardiovascular disease (CVD) is the most common cause of death among Europeans: more than 4 million people die of CVD every year in Europe (~45% of all deaths) [1,2]. Disorders of the autonomic nervous system (ANS) have a key pathophysiological role in early stages of essential hypertension [3,4], myocardial infarction [5,6], and chronic heart failure (CHF) [7–10], producing coronary vasoconstriction, increasing cardiac oxygen consumption and leading to fatal events [11–13]. The clinical importance and prognostic implications of the exaggerated sympathetic nervous system (SNS) are well documented in CVD [14,15] in that it is a known trigger of cardiac arrhythmias and sudden death [16–19]. The activity of the central nervous system also seems to play a role in sympathetic hyperactivity [20,21] and is accompanied by humoral overactivity of the renin–angiotensin–aldosterone system (RAAS) [9,22]. In the long term, sympathetic chronic stimulation is deleterious [14,23]. In the periphery, tubular fluid level and sodium reabsorption increase in response to RAAS activation [24] and peripheral arterial resistance increases [25], thereby increasing cardiac pre- and postload. In addition, sympathetic hyperactivity alters myocardial calcium cycling, which is responsible for reduced myocardial contractility [26]. The spontaneous activity of certain slow calcium channels (L-type) could explain in part ventricular arrhythmias and cardiac sudden death [17].

Pharmacological treatments for CVD need to decrease the overactivity of the SNS (β blockers, angiotensin-converting enzyme inhibitors, etc.) [27,28] and to increase the activity of the parasympathetic nervous system (adenosine, cholinesterase inhibitors, statins) [29]. Additionally, different non-pharmacological techniques have the same goal, such as vagal stimulation, renal denervation and carotid baroreceptor stimulation, and were well described in a recent review [30]. Among the non-pharmacological techniques, ET is of growing interest in major

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CVD guidelines. With an IA level of evidence for the latest recommendations from the European Society of Cardiology and an IB level from the American Heart Association, ET has become one of the pillars of CHF treatment and coronary heart disease (CHD) [31–35]. The therapeutic potential of restoring or enhancing the cardiac vegetative balance with ET is very promising [36–38], but the underlying mechanisms are still unclear.

This review aims to summarize some of the beneficial effects of aerobic ET on CVD and place sympathovagal balance as an essential element to be considered in management for patients who benefit from a cardiac rehabilitation program.

2. Effect of ET on the autonomic nervous system

2.1. Muscle sympathetic nerve activity

Muscle sympathetic nerve activity (MSNA) is a neurophysiological method (microneurography) that allows for recording sympathetic nerve traffic. MSNA is markedly increased in patients with CHD [39,40] (45 ± 2.3 vs. 31 ± 1 bursts/min; $p < 0.001$), hypertension [41,42] (33.3 ± 1.7 vs. 23.9 ± 1.6 bursts/min; $p < 0.01$ respectively), and CHF [43] (62 ± 4 vs. 39 ± 4 bursts/min; $p < 0.01$) as compared with healthy subjects, but MSNA can be decreased by ET [44,45]. The research team from the Heart Institute of University of Sao Paulo has spent more than 10 years investigating the effects of ET on MSNA in CHF and CHD patients [46–51]. The team demonstrated that regular ET can normalize the basal overactivation of the sympathetic nerve (Table 1). After 4–6 months of ET (3 supervised 60-min exercise sessions/week of cycling and strengthening), baseline values of MSNA (about 45 bursts/min for CHF patients) decreased significantly to within normal values relative to healthy participants (about 30 bursts/min) [46–51], with no change in untrained groups. Furthermore, ET had no gender- or age-specific effect on MSNA.

2.2. Heart rate variability (HRV)

HRV is a non-invasive reproducible measure of ANS function corresponding to the balance between sympathetic and parasympathetic effects on the sinoatrial node rate [52–54]. HRV indexes are highly decreased in CVD patients and predict poorer outcomes, such as reduced left-ventricular function and sudden cardiac death [38,55–58]. The risk of all-cause and progressive heart failure death was increased with a standard deviation of normal to normal R-R intervals (SDNN) of <67 ms (relative risk [RR] 2.5; 95% CI 1.5–4.2) [56]. In a retrospective analysis of 1284 CHD patients, SDNN values <70 ms significantly and independently predicted cardiac mortality (RR 3.2; 95% CI 1.6–6.3) [59]. According to Bilchick et al. [58], each increase of 10 ms in SDNN conferred a 20% decrease in risk of mortality ($p = 0.0001$) with an increase in vagal tone and a decrease in sympathetic activity [38,60–65]. In a recent randomized controlled, single-blinded trial, Murad et al. [64] included 66 CHF patients (mean age 69 years, New York Heart Association [NYHA] class II–III) with preserved or reduced ejection fraction.

Table 1
Effect of exercise training on muscle sympathetic nerve activity (MSNA) in patients with chronic heart failure (CHF) and post-acute coronary syndrome (post-ACS) from the literature.

References	No. of patients	Patient characteristics	Training protocol	MSNA basal values	MSNA post-training values
CHF patients					
Antunes-Correa, 2012	52	45–59 years Trained ($n = 16$) vs. untrained ($n = 17$) 60–75 years Trained ($n = 11$) vs. untrained ($n = 8$)	4 months 3×60 min/week Stretching Cycling Strengthening Intensity: anaerobic threshold up to 10% below the respiratory compensation point	43–50 bursts/min according to the group with no difference between them	In trained groups: 27–29 bursts/min ($p < 0.001$) Unchanged in untrained groups No age effect ($p = 0.69$)
Antunes-Correa, 2010	40	57–60 years Men exercise-trained ($n = 12$) Men untrained ($n = 10$) Women exercise-trained ($n = 9$) Women untrained ($n = 9$)		43–50 bursts/min according to the group with no difference between them	In trained groups: 30 bursts/min ($p < 0.001$) Unchanged in untrained groups No gender effect
Roveda, 2003	16	35–60 years Exercise-trained ($n = 7$) Sedentary control ($n = 9$)		40–50 bursts/min	In reply to: trained groups ~30 bursts/min ($p < 0.001$) Unchanged in untrained groups HF trained group did not differ from trained healthy control group after training
Fraga, 2007	27	Exercise training ($n = 15$) Untrained control ($n = 12$)		45 bursts/min	In trained group: 35 bursts/min ($p = 0.001$) Unchanged in untrained groups
Mello Franco, 2006	29	Untrained control ($n = 12$) Exercise trained ($n = 17$)		43–45 bursts/min	In trained group: 35 bursts/min ($p = 0.007$) Unchanged in untrained groups
Post-ACS patients					
Martinez, 2011	28	Exercise trained ($n = 14$) Untrained control ($n = 14$)	6 months/3×60 min/week Stretching/cycling/strengthening/anaerobic threshold	42–45 bursts/min	In trained group: ~20 bursts/min ($p < 0.001$) (similar to healthy control group) Unchanged in untrained groups

After 16 weeks of follow-up, the supervised ET group showed significantly greater increase in both SDNN and root mean square successive difference (a time domain measure of heart period variability) as compared to controls (+15.46 vs. +2.37 ms, $p = 0.016$, and +17.53 vs. +1.69 ms, $p = 0.003$, respectively). This finding may indicate a favorable effect of ET on prognosis for CHF patients. Larsen et al. [63] evaluated the correlation between HRV index and survival. For this, 12 CHF patients (mean age 67 years; NYHA class III) underwent a 12-week rehabilitation program. After 87 months of follow-up, survivors and non-survivors showed borderline significant differences in temporal variables of HRV after training ($+10.4 \pm 8.45$ vs. -2.7 ± 10.2 ms, $p = 0.053$). Only survivors showed a significant increase in SDANN-i after ET (107.9 ± 40.6 vs. 118.3 ± 48.1 ms, $p = 0.029$). In CHD patients, the results were heterogeneous and the resting HRV index often remained unchanged after the cardiac rehabilitation program. For example, Duru et al. [66] found unchanged basal HRV indexes after 8 weeks of aerobic exercise (at 70% of HR reserve) in 25 patients with post-acute coronary syndrome (post-ACS). La Rovere et al. [67] studied HRV indexes in 22 trained and untrained CHD patients by the head-up tilt test. Frequency domain HRV indexes at rest were not changed after a 4-week training program. Nevertheless, during the head-up tilt test, trained patients showed significantly greater increases in low-frequency power (LFnu) ($84 \pm 3\%$ vs. $69 \pm 5\%$) and decreases in high-frequency power (HFnu) ($7 \pm 1\%$ vs. $19 \pm 4\%$) than controls. With orthostatic stress (such as a tilt test), the baroreceptors are stimulated to drive an increase in sympathetic vasoconstrictor outflow and a reduction in vagal tone. Therefore, in post-ACS trained patients, the reflex activity of the autonomic pathways may have been improved. Of note, the HRV index could be improved early in post-ACS patients with ET. In a very short ET program, 5 days, in phase I cardiac rehabilitation, Santos-Hiss et al. [68] highlighted that trained patients in the resting position showed increased HFnu after training ($35.9\% \pm 19.5\%$ to $65.19\% \pm 25.4\%$, $p = 0.002$) and decreased LFnu ($58.9\% \pm 21.4\%$ to $32.5\% \pm 24.1\%$, $p = 0.024$) and LF/HF ratio (3.12 ± 4.0 to 1.0 ± 1.5, $p = 0.004$), with no changes in controls.

2.3. Arterial baroreflex function

Arterial baroreceptors (located in the aortic arch and carotid sinuses) are the starting point of nervous afferences playing a constant inhibitory role in decreasing SNS activity [69–71]. Defective arterial baroreflex is well known to contribute to sympathetic overactivity [9,72–75]. The studies of La Rovere et al. underlined that arterial baroreflex is a powerful predictor of cardiovascular death, with <3.0 ms/mmHg associated with increased risk of cardiac mortality, by 2.8-fold (95% CI 1.24–6.16) [74,76]. Several mechanisms could explain this impairment: reduced sensitivity of the baroreceptor afferent fibers [77–79] mediated in part by reduced expression and activation of the voltage-gated sodium channels [80] and in part by elevated plasma aldosterone content, which reduces afferent discharge sensitivity [81], and deterioration of the central autonomic pathways that mediate the baroreflex [82,83]. Baroreflex function is improved with ET in animal studies [84–86]. In CHF patients, ET seems to improve arterial baroreflex function [65,87] or prevent its deterioration [88]. In 12 patients with CHF (mean age 58 years, left-ventricular ejection fraction 36%, NYHA class II-III), Pietila et al. studied the effects on baroreflex sensitivity (among other things) of a 6-month ET protocol comprising light-intensity circuit muscle training and aerobic cycling once a day for 6 days/week. At the end of the program, baroreflex sensitivity increased by 74%, from 5.83 ± 0.82 to 10.15 ± 1.66 ms/mmHg ($p < 0.05$). The most recent study investigating the effect of ET on the arterial baroreflex control of MSNA (ABR_{MSNA}) in CHF was conducted by the Heart Institute of the University of Sao Paulo [89]. The authors studied the impact of 4 months of exercise on the magnitude and latency of the arterial baroreflex response. For this, 26 CHF patients (NYHA class II-III, left-ventricular ejection fraction $\leq 40\%$) were randomized to undergo no training or an ET program. The ET protocol was in line with the group's other studies (4 months, 60 min/day, 3 times/week). The gain and time delay of ABR_{MSNA} were unchanged with training, and with no training, the baseline values worsened at 4-month follow-up (gain and time delay values of ABR_{MSNA} before and after the 4-month follow with no training were 3.5 ± 0.7 vs. 1.8 ± 0.2, a.u./mmHg, $p = 0.04$, and 4.6 ± 0.8 vs. 7.9 ± 1.0 s, $p = 0.05$, respectively). The authors concluded that the reduced sympathetic nerve activity was mediated by an increase in arterial baroreflex sensitivity but also may be modulated by chemoreflex control and/or ergoreflex control.

In the same way, baroreflex gain was decreased after myocardial infarction. In 2011, Martinez et al. [51] showed that at 3 months after ACS (2 months of ET), baroreflex control increased from 6.0 to 15.6 ms/mmHg with ET. This benefit was even greater at 7 months after ACS (6 months of ET), when baroreflex control in this group was 18.5 ms/mmHg and similar to that in healthy controls (16.4 ms/mmHg). Untrained post-ACS patients did not show any improvement in the baroreflex sensitivity variable during 7 months of follow-up, despite the same clinical management. In this context, ET based on 3 times/week for 6 months restored baroreflex sensitivity in patients with myocardial infarction, for a long-term protective effect of ET in these patients.

2.4. Resting HR and HR recovery

Epidemiological studies have confirmed that an elevated resting HR reflects greater neurohormonal activation and is an independent predictor of cardiovascular and overall mortality in the general population and in patients with CVD [90–96]. In addition, a high resting HR affects ischemic episodes that may trigger arrhythmias [93,97]. Lowering the HR to about 60 beats/min [98] with pharmacological treatments reduced overall and cardiovascular-related mortality [93,97,99,100]. ET in patients with CVD appears to be efficient in lowering resting HR and increasing chronotropic reserve [101–103]. For example, after a 2-month residential rehabilitation program, resting HR decreased by 11 beats/min in a CHF exercise group [104]. HR recovery after a maximal exercise stress test is considered a vagal tone indicator. The increase in HR is first due to withdrawal of parasympathetic activity with lower intensity, then, with moderate and high intensity, is due to a sympathetic activation [53]. Just after peak exercise, HR drops during the first seconds and minutes because of parasympathetic reactivation with the decrease, then sympathetic inactivation [53]. HR recovery is considered an indicator of vagal tone [105] and a strong prognostic factor of cardiovascular events and death in healthy people and CHF patients [91,101,104,106,107] as well as patients with coronary artery disease [106,108,109]. In CHF, HR recovery is altered, with parasympathetic and baroreflex dysfunction [110,111]. Nonetheless, ET studies reported improvements in HR recovery [104,112] in patients with CHF and CHD [113,114]. In 2007, Myers et al. [104] showed that HR recovery was significantly faster in the exercise group from minutes 2 to 6 after a 8-week training program as compared to the sedentary control group (ANOVA main effect in trained subjects 12.6 beats/min, $p < 0.001$; main effect among controls 2.6 beats/min, $p = 0.27$; between-group interaction $p = 0.005$). Resting HR and HR recovery were enhanced with an ET, presumably because of impaired vagal tone [115]. In consequence, with a lower resting HR and a better HR recovery after exercise, HR reserve is increased, for better sympathovagal balance and improved survival for patients with CVD.

3. Physiological mechanisms underlying the effects of ET on ANS

The physiological mechanisms contributing to improved sympathovagal balance are multiple and have not yet been fully defined. Many studies have investigated changes in plasma catecholamine levels after ET programs in CHF and have shown encouraging results, with a decrease in levels at rest and during submaximal exercise [103,116]. Recently, Rengo et al. [103] investigated the impact of a 3-month ET program on changes in plasma level of norepinephrine, serum level of N-terminal pro-brain natriuretic peptide and mortality over a mean follow-up of 27 months. The authors enrolled 221 CHF patients (mean age 72 years, mean left ventricular ejection fraction 32%). The 3-month training protocol (30 min of cycling 3 times/week at 60–70% peak VO_2) decreased plasma norepinephrine level (642–578 pg/mL, $p < 0.0001$), N-terminal proBNP level (2111–1532 pg/mL, $p < 0.0001$), and HR (83.6–69.2 bpm, $p < 0.0001$). Change in resting plasma norepinephrine level was the most powerful predictor of cardiac mortality at 27-month follow-up (hazard ratio 38.7, $p < 0.0001$). Furthermore, when the authors stratified patients by median values of Δnorepinephrine level (% changes), mortality rate was higher for patients with Δnorepinephrine level below than above the median (87% vs. 4%). Furthermore, ET induced neuromodulation in both the peripheral and central levels. Patel et al. investigated how ET could normalize the central sympathetic outflow in rats with heart failure. Their results suggested a positive central modulation in the inhibitory and excitatory pathways (for details, see review [117,118]) via increased nitric oxide level in the paraventricular nucleus and reduced central angiotensin II level that contributed to sympatho-inhibition and sympatho-excitatory paths, respectively, in brain areas [119]. Aerobic ET in CHF and in hypertensive rats could be efficient as renin–angiotensin system blocker therapy to reduce the brain renin–angiotensin system activity and to decrease arterial pressure as well as sympathetic overactivity [120,121].

4. Alternative interventions to traditional ET

Most studies investigating the effects of ET on ANS activity in CVD are based on continuous moderate aerobic exercise. Little is known about the effects of high-intensity interval training combined or not with other activities such as relaxation and breathing exercises or electrical stimulation. In this section, we discuss the importance of these different types of activities and their positive effect on the sympathovagal balance.

4.1. High-intensity interval training (HIIT)

The latest recommendations suggest interval training (IT) for heart failure patients [122–124] and CHD [125]. HIIT is defined as repeated short-intensity bouts (e.g., 30–60 s at 90–100% peak exercise capacity) interspersed with a recovery period (30–120 s at 50% peak exercise capacity or passive recovery). HIIT may be more effective than moderate intensity and continuous exercise (MICE) for improving exercise capacity, quality of life, maximal oxygen consumption (VO_{2max}) and cardiac remodeling in CHD and CHF patients [126–128]. In a recent review [129] of HIIT in cardiac rehabilitation programs (phase II and III), Gayda et al. discussed the interest of developing progressive models of ET based on HIIT combined with other forms of exercise sessions such as MICE, resistance training or inspiratory muscle training.

In healthy subjects, ANS responses differ by exercise modality (duration, frequency, intensity, recovery, volume). Therefore, our team studied an optimized and safe HIIT model [130–132]. In 2013 [133], we studied the effect of one session of HIIT on ANS activity while ensuring security and patient comfort [130]. Our hypothesis was that HIIT would enhance vagal tone and thus reduce the likelihood of arrhythmic events in CHF. Eighteen CHF patients underwent a baseline assessment (control condition) and were randomized to a single session of HIIT (repeated 30 s of exercise at 100% peak power alternating with phases of 30 s of passive recovery) and to isocaloric MICE. As compared to control and MICE conditions, a single session of HIIT significantly increased parasympathetic tone. The normalized HF power measured by 24-h electrocardiography for the 3 conditions was 31.56%, 24.61% and 35.95%, respectively ($p < 0.01$). After HIIT, the number of premature ventricular contractions decreased significantly (531 vs. 1007 and 1671 for control and MICE, respectively, $p < 0.01$). We found a correlation between changes in premature ventricular contraction and LF/HF ratio ($r = 0.66$, $p < 0.01$) in patients exposed to HIIT. Passive recovery with each 30 s may have led to "a vagal training stimulation" and the beneficial effects on HRV and PVC are probably related to this specific mode of HIIT, which suggests sympathovagal balance resetting in the postexercise period. The clinical importance of premature ventricular contractions (and HRV) in CHF is a powerful predictor of cardiovascular mortality [134]. Furthermore, according to patients, HIIT was the most preferred protocol, associated with lower perceived exertion as compared with MICE, and no adverse event was reported by health care providers or patients. Other studies reported improvements in HRV after HIIT in cardiac patients [135] and in patients with type 2 diabetes mellitus [136]. However, the study of Currie et al. [137] reported no improvement in HRV index and HR recovery in CHD patients after a 12-week ET of HIIT or MICE despite an increase in VO_{2peak} in the 2 groups (+20% $p < 0.001$, with no difference between them). The authors suggested that the length of recovery between ACS and the beginning of training (5–6 months), the optimal medical management, and the normative baseline values contributed to this lack of significant change in autonomic nervous activity.

These results highlight the positive benefit–risk ratio associated with HIIT and suggest that this type of intervention could reduce the cardiovascular risk. Nevertheless, the long-term effects of HIIT remain to be studied.

4.2. Breathing exercises or relaxation

Respiratory sinus arrhythmia–biofeedback or heart rate variability–biofeedback involves the lowering of the breathing rate to the frequency at which the amplitude of HRV is maximized. This breathing exercise stimulates the baroreceptor [138,139], thereby modulating the sinus rhythm to enhance sympathovagal balance and cardiovascular risk factors [140], including in CVD [139,141, 142]. In the Bernardi et al. study [142], 81 patients with CHF and 21 healthy controls underwent electrocardiography, respiration, and blood pressure measurement during 5 min of spontaneous breathing, 4 min of controlled breathing at 15 breaths/min (corresponding to spontaneous breathing) and 4 min of controlled breathing at 6 breaths/min. The slow breathing rate in the CHF group increased the mean RR interval to 20 ms, decreased both systolic and diastolic blood pressure (systolic, from 117 to 110 mmHg, $p < 0.009$; diastolic, from 62 to 59 mmHg, $p < 0.02$) and significantly increased the baroreflex sensitivity (from 5.0 to 6.1 ms/mmHg, $p < 0.0025$). The recent first systematic review of the effect of relaxation and meditation on symptom management strategies in CHF [143] found symptom-related quality of life improved with this approach, as well as pain, dyspnea, fatigue, and sleep disturbance.

Breathing techniques, relaxation exercises or some types of meditation have a favorable impact on parasympathetic and

sympathetic activity (for review [144]), with increased HF power and decreased LF/HF ratio. In the Curiati et al. study [145], 19 older patients with optimally treated CHF were randomized into 2 groups: a meditation group (who listened to a 30-min audiotape twice a day for 12 weeks and attended a weekly meeting) or a control group (who just attended a weekly meeting). Norepinephrine level was reduced in the meditation group alone (from 677.7 to 387.1 pg/mL, $p = 0.008$), which suggests reduced SNS activity, and were unchanged in the control group.

4.3. Transcutaneous electrical nerve stimulation (TENS)

TENS is classically used to stimulate large myelinated afferent fibers, used in pain treatment, whereas neuromuscular electrical stimulation (NMES) stimulates efferent fibers, causing muscular contraction. For the first time, our group provided evidence that TENS could directly reduce sympathetic activity (measured by MSNA) in patients with CHF in a randomized, sham-controlled, double-blind study (EMSICA Study [146]). We recruited 22 CHF patients (NYHA class III): 11 underwent TENS, and 11 NMES. Each of the protocols was cross-over, randomized and sham-controlled. MSNA was recorded immediately after electrical stimulation cessation on the opposite stimulated limb. Compared to sham stimulation, both TENS and NMES reduced MSNA (69.7 vs. 63.5 bursts/min, $p < 0.01$ after TENS and 56.7 vs. 51.6 bursts/min, $p < 0.01$ after NMES). These findings highlight the clinical importance of this non-pharmacological therapy based on ET for long-term treatment of patients with myocardial infarction. Reduced MSNA by TENS could be attributable to enhanced spontaneous baroreflex sensitivity; As well, the ergoreflex induced by TENS could stimulate the nucleus tractus solitarius and the release of substance P, which could interact with baroreflex sensitivity and decreased sympathetic outflow [147].

5. Perspectives

Several reports support evidence for an association between parasympathetic factors and training level [148,149]. These data are available for trained people or athletes but not patients with CVD. In the field of high sport performance, ET programs are individualized to optimize physiological adaptations (e.g., VO_{2max}, metabolic or cardiac recovery) and consider physiological variables related to the athletes. With this in mind, some authors have proposed that outcomes of cardiac ANS activity would be an efficient tool for individualized training prescription and induced long-term physiological benefit [149–151]. In view of this suggestion, an interesting review by Stanley et al. [149] recommended that training (not only for highly trained but also inactive people) could be structured with weekly micro-cycles to improve cardiovascular fitness or cardiac recovery or induce an overload of training to progress fitness. For example, to maximize recovery, the period of rest and low-intensity training sessions are increased and the frequency of high-intensity training sessions is reduced, each separated by at least 48 h of recovery to allow for beneficial compensation of the cardiovascular and autonomic systems. While improving cardiovascular fitness, the weekly micro-cycle is structured with consecutive high and moderate intensity training followed by a rest day to induce improvement. In our clinical experience, all patients perform the same daily ET session to a target HR corresponding to 70% of HR reserve ±5 beats/min. Sometimes, high-intensity interval training is used (but this mode is not systematized and depends on physiotherapist practice). Adapting the recommendations of Stanley et al. (2013) would be of interest to investigate the effect of an individualized ET program based on HRV outcome as previously described.

In CHF, one study [152] found lower pre-training HRV index associated with less improvement in physical capacity after a cardiac rehabilitation program. In this observational, non-randomized study, 57 CHF patients (left ventricular ejection fraction <35%)

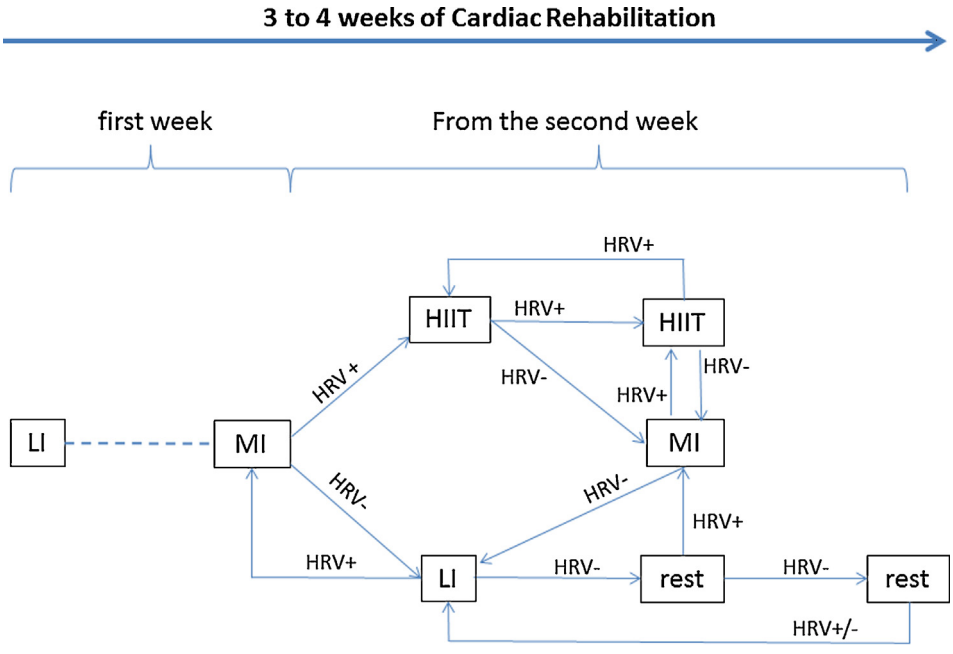

Fig. 1. A decision tree for prescribing exercise according to heart rate variability (HRV) indexes in cardiac patients. During the first week of cardiac rehabilitation, the exercise training (ET) sessions are set at low intensity and increase gradually to moderate intensity. From the second week, the exercise intensity is prescribed according to HRV indexes (high-frequency [HF] power and ratio of low-frequency [LF] to HF). The first reflects effects on vagal tone and the second, sympathovagal balance. When HRV indexes increase or remain stable (HRV+), the training intensity increases; when HRV indexes decrease (HRV−), the training intensity decreases. The rate of perceived exertion (Borg scale [154]) must also be considered. LI: low intensity; MI: moderate intensity; HIIT: high intensity interval training. HRV+ is defined as an increase in HF power and a decrease in LF/HF ratio; HRV− is defined as a decrease in HF power and an increase in LF/HF ratio.

performed a 6-min walk test and a maximal cardiopulmonary exercise test before and after 2 weeks of training; HRV was evaluated by 24-h-electrocardiography–Holter recordings. According to pre-training SDNN values, patients in the first quartile (55 ms) showed a significantly lower VO_2 peak (11.4 ml/min/kg) that those with higher SDNN values (>16 ml/min/kg) ($p = 0.015$). The authors concluded that the pre-training HRV index could help identify patients who need specific individualized training to improve cardiovascular capacity. In other words, the HRV index could be helpful to distinguish "responders" and "non-responders" to an ET program, with more attention to the first type. With the concept of a weekly micro-cycle described by Stanley et al., patients could benefit from a session of HIIT or low intensity, or rest, depending on their HRV values.

In healthy males, Kiviniemi et al. [153] investigated a 4-week endurance ET program based on daily HRV index. Participants were randomized to a predefined training group ($n = 8$), an HRV guided training group (HRV, $n = 9$) or a control group ($n = 9$). With a maximum of 2 consecutive high-intensity sessions or resting sessions, the daily training sessions of the HRV group were guided by a daily morning measurement of the HRV index for 10 min. If HFnu did not change or was increased (as compare to individual reference values), the training session was set at high intensity, and if HFnu was decreased significantly, low-intensity training or resting was prescribed (Fig. 1). After the 4-week training, VO_{2max} increased only in the HRV group (+4 ml/min/kg, $p = 0.002$). The authors concluded that daily HRV measurements may help determine the type of exercise session (low or high intensity or rest) based on the status of autonomic regulation. Knowing that cardiac patients present wide heterogeneity in response during cardiac rehabilitation (revealing even negative changes or non-response), this easy-to-use tool would be useful for daily training prescription and supervision during cardiac rehabilitation. On the basis of the "HRV guided training group" of Kiviniemi et al., we propose a decision tree to prescribe exercise based on HRV in cardiac patients (Fig. 1). Indeed, this model remains theoretical and has not been tested in cardiac patients.

In cardiac rehabilitation centers, the optimal ET program to improve clinical values must consider individual characteristics of patients; exercise prescribers should be adequately trained to adapt the features of physical exercise sessions to each patient according to their needs, desires and physiological values.

In this context, the use of HRV has become an approach to fatigue well inspired by the concept derived from sports science, which uses the HRV-vagal index to manage exercise sessions. To monitor patients on Monday (after the weekend), a valid score must consider the medication, sleep quality, blood pressure and other factors associated with HRV. This score could guide the exercise prescribers who anticipate an overload of exercise resulting in fatigue or otherwise detecting the possibility of increasing the safe workload.

6. Conclusions

Overall, ET, associated with other non-pharmacological strategies, may positively affect the ANS by increasing vagal modulation and decreasing sympathetic tone. Further research is needed to identify the exercise regimen (i.e., duration and intensity) that produces optimal improvements in HRV. Furthermore, the use of HRV indexes to prescribe, monitor and supervise the ET of patients referred to a cardiac rehabilitation program should be proven and established.

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The authors declare that they have no competing interest.

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