Comparison of Acute Response of Cardiac Autonomic Modulation Between Virtual Reality-Based Therapy and Cardiovascular Rehabilitation: A Cluster Randomized Crossover Trial

Paula F. Silva[1*], Ana Laura Ricci-Vitor[1], Mayara M. A. Cruz[1], Giovanna L. B. Borges[1], David M. Garner[2], Luiz C. M. Vanderlei[1]

[1]Department of Physiotherapy, São Paulo State University (UNESP), School of Technology and Sciences, Presidente Prudente, Brazil; [2]Cardiorespiratory Research Group, Department of Biological and Medical Sciences, Faculty of Health and Life Sciences, Oxford Brookes University, Headington Campus, Gipsy Lane, Oxford OX3 0BP, United Kingdom.

*Corresponding author: Paula F. Silva. Department of Physiotherapy, São Paulo State University (UNESP), School of Technology and Sciences, Presidente Prudente. Roberto Simonsen St, 305, Educational Center, Presidente Prudente, SP, BR. 19060-900. E-mail: silva.pf@live.com

ABSTRACT

OBJECTIVE: To assess the acute response of cardiac autonomic modulation (ACAM) during and after a session of virtual reality-based therapy (VRBT) compared to a session of conventional cardiovascular rehabilitation (CR) and to evaluate the effects of 12 weeks of training on this response. **METHODS:** We assessed 28 volunteers (63.39±12.48years). The ACAM was judged by linear indexes of heart rate variability (HRV) in VRBT and CR sessions. Later, patients completed 12 weeks of VRBT+CR and the assessment was repeated at the 12th week. **RESULTS:** Throughout the 1st VRBT session vagal withdrawal occurred (RMSSD/HFnu); sympathetic nervous system stimulation (LFnu) and progressive decrease of global HRV (SDNN). During the recovery, the SDNN, HFnu and LFnu improved from the 5thminute on both therapies. After 12 weeks, the LFnu, HFnu and the LF/HF-ratio revealed no significant changes in Ex3-Ex4 equated to Rep during VRBT. In recovery, the HFnu and LFnu improved before the 5thminute on both therapies. **CONCLUSIONS:** ACAM during and after the VRBT was comparable to CR, yet, the extents were greater in the VRBT. After 12 weeks of VRBT training, the subjects adapted to the exercises from the 15thminute and exhibited faster recovery of HFnu and LFnu indexes compared to the 1st week.

Keywords: cardiac rehabilitation; virtual reality exposure therapy; sympathetic nervous system; exercise; cardiovascular diseases.

INTRODUCTION

Cardiovascular rehabilitation (CR) has established effectiveness, with several advantages, for instance, reduction in the duration of hospital stays and lessened cardiovascular risks. There is an earlier return to employment, functional and hemodynamic improvements and elevated psychological and social welfare (Cowie *et al*, 2019; Hegewald *et al*, 2019; Muela, Bassan, and Serra, 2011; Oliveira, 2016; World Health Organization, 1964).

Despite this, cardiovascular diseases (CD), remain the leading cause of morbidity, mortality and general socio-economic burden (Guimarães *et al*, 2015; World Health Organization, 2018). Still, the patient's compliance with the CR program is low, thus a challenge for treatment. New ways that increase patient compliance are currently being deliberated (Ades *et al*, 2017; Bennett *et al*, 2019; Supervia *et al*, 2017). This scenario of innovative CR techniques could be preferred to the conventional techniques for motivating patient participation provided on the condition that their effectiveness in relation to the CR objectives is not compromised.

In this way, the Virtual Reality-Based-Therapy (VRBT) is a type of treatment whereby the patient practices the virtual environment of interactive games and emerges as an up-to-the-minute technique that can be enforced to the CR to accomplish physical exercises. Amongst its benefits, it has superior variability and adaptability, clear data storage, online remote data access, reductions in size of the hardware, for instance smartphones, above and beyond stimulating motivation (Burdea, 2003).

By reason of its intrinsic flexibility and adaptability, it can be applied throughout all stages of the CR. In their phase I study, Cacau *et al.* (2013) recorded earlier recovery and hospital discharge because of less pain, a greater ability to walk and higher-energy levels. For patients eligible for phase II CR, VRBT using the projection of images associated with treadmill training promoted improved chronic hemodynamic effects in maximum heart rate, peak oxygen consumption (VO2peak), peak metabolic equivalents and anaerobic threshold; than exercise on a treadmill alone (Chuang, 2005; Chuang 2006). Additionally, incorporating VRBT into a CR program permitted the patients to achieve their rehabilitation goals (85% of maximum heart rate or 75% of VO2peak) in a lesser number of sessions (Chuang 2006). In the phase III the VRBT had enhanced selective attention and conflict resolution ability of the participants, revealing the potential of CR to improve the executive function (Vieira, Melo, Machado, and Gabriel J, 2018).

The VRBT promoted a significant increase in physical activity and energy expenditure produced above and beyond the improvement of the motivational factor (García-Bravo *et al*, 2019). Santana *et al.* (2016) reported similar blood pressure and HR in sedentary adults, when comparing aerobic exercise programs performed on the exercise bike or using Nintendo Wii games. Thus, the VRBT can be applied accompanied by the prevention of risk factors (RF). Yet, despite the likely advantages that VRBT can encourage, it is vital to understand whether the acute effects of this therapeutic modality are comparable to those attained with conventional CR. Cruz *et al.* (2020) observed that a VRBT session produced similar physiological acute hemodynamic effects to those obtained in CR. Considering that the autonomic nervous system (ANS) is at best partially responsible for regulating some cardiorespiratory variables; studying the ANS performance is important. This system can be assessed by heart rate variability (HRV), a simple, low-priced and non-invasive technique to measure autonomic impulses (Vanderlei *et al*, 2009; Vanderlei *et al*, 2015).

It is imperative to highlight that in healthy persons, VRBT by simulation was demonstrated to be safe and obeyed the guidelines of the American College of Sports

Medicine (ACSM) (Guderian *et al*, 2010; Malinska, Zuzewicz, Bugajska, and Grabowski, 2015; Monteiro-Junior *et al*, 2014). But, in patients exhibiting cardiac diseases, who require greater manipulation of cardiovascular parameters, since high responses may cause greater risk to the individual's health (Rodgers *et al*, 2000), the acute responses triggered by VRBT practice have not been fully investigated. In this way, studying the autonomic responses to VRBT by simulation with photographic and video devices is essential to ensure safety and effectiveness of the application of this modality in these patients.

Some gaps in our knowledge can be highlighted in this regard: What is the acute response of cardiac autonomic modulation (ACAM) during a session using VRBT? Are these responses analogous to the CR responses? After 12 weeks of training, what happens with the ACAM? This study was designed to answer these questions.

Therefore, the study's objectives were to evaluate the ACAM during and after a session of VRBT compared to session of conventional CR and to examine the effects of 12 weeks of training on this response.

MATERIALS AND METHODS

Design

This was a cluster randomized crossover trial, that involved five days of evaluation and 12 weeks of training associating VRBT with CR. On the first day, patients completed an initial evaluation for identification and characterization. During this initial evaluation an anamnesis was performed, including age, gender, diagnosis, presence of RF and comorbidities, presence of signs and symptoms, and pharmacotherapies taken. Additionally, anthropometric evaluation was commenced to compute and benchmark body mass index (BMI) (World Health Organization, 2000) and the following cardiorespiratory parameters were evaluated: HR, systolic blood pressure, diastolic blood pressure, respiratory rate and peripheral oxygen saturation.

On the second and third days of evaluation they performed two randomized sessions (VRBT or CR). The evaluations were on non-consecutive days in the same week and the participants held the two sessions in pairs. After this, patients were submitted to 12 weeks of VRBT with CR for three times a week, with, two sessions of CR and one session of VRBT. Then, in the 12^{th} week, we performed the fourth and fifth day of evaluation that repeated the second and third day procedures to investigate the acute autonomic impact after the training. The schematic figure for this study is exemplified in Figure 1.

 # INSERT FIGURE 1 #

Casuistry and scenario

Patients from the Cardiology Division of the Center for Physical Therapy and Rehabilitation Studies and Treatment of the São Paulo State University (UNESP), School of Technology and Sciences, Presidente Prudente, São Paulo, Brazil, were invited to participate in this study. Entry criteria included volunteers over 18 years old, male or female, with a diagnosis of CD or cardiovascular RF, who attended the standard program of CR for at least three months. Participants were excluded from the study if they presented vital changes in sense of balance, defined by being unable to perform treadmill walking during a CR program, problematic symptoms or indications throughout the conventional session, degenerative diseases, individuals that declined study participation, or that failed to complete all the necessary stages, or presented errors greater than 5% on the HRV record (Godoy, Takakura, and Correa, 2005; Vanderlei *et al*, 2009; Catai *et al*, 2020).

Following an initial invitation and evaluation of their eligibility, subjects were informed about the research objectives, and if approved, signed a confidential written informed consent statement inclusive of the research proposal. The recruitment occurred between April and July 2017 and, the protocol was completed between August and December 2017. The trial was uninterrupted. Also, the local ethics committee permitted all procedures under CAAE number: 69406017.2.0000.5402 and all procedures were conducted according to the Helsinki Declaration. This study was part of the research registered by the code NCT03377582 on the ClinicalTrials.gov platform.

Interventions

The volunteers completed a CR session and VRBT session. Their sequences were randomized on the first day by www.randomization.com (Dallal, 2007). Sessions were directed by two physiotherapists who specialize in CR and completed the training using VRBT. Interventions were completed during the morning in a quiet laboratory with temperature between 21ºC and 24ºC and relative humidity between 40% and 60%.

Each assessed session had a mean duration of 85 minutes (min), comprising of four phases: initial rest, warm-up, conditioning, and recovering. The initial rest stage was performed with volunteers flat on mats breathing naturally for 10 min to stabilize hemodynamic values. The warm-up persisted for 15 min; the conditioning phase continued for 30 min. There was a specific protocol for each therapeutic modality (CR and VRBT); as described later. The recovery phase was completed with volunteers' supine breathing naturally for 30 min to follow up the recovery (Brazilian Society of Cardiology, 1997).

The CR sessions' intensity was identical to that in the conventional CR program, which, except for clinical and/or physical limitations, prescribed between 40% to 70% of

Heart Rate Reserve (HRR) for patients with CVD and 60% to 80% HRR for those with cardiovascular RF (Mezzani *et al*, 2013) Similarly, for the control of intensity, the Borg scale was consulted (Borg, 1982). Throughout this session, the target intensity, supervised by the Borg scale, was between 12 and 16 (Mezzani *et al*, 2013).

Following the evaluation sessions, the volunteers were submitted to 12 weeks of CR+VRBT at a frequency of three times a week, with two sessions of CR and one of VRBT always in the same sequence. The training sessions persisted for 50 min, entailing three phases: the warm-up phase for 15 min; conditioning for 30 min and; relaxation for 5 min. To conclude, at the end of the training protocol, the evaluations were repeated with sequences randomized (Dallal, 2007). All patients performed both evaluation sessions, and if unavailable, the physiotherapist re-scheduled their session.

Conventional therapy

In the CR warm-up stretching and whole-body exercises of upper limbs, lower limbs and combined exercise were completed. The conditioning phase involved performing exercises on a treadmill with individually adjusted speed and inclination to maintain the effort within the pre-established intensity (Mezzani *et al*, 2013).

Virtual Reality-Based Therapy (VRBT)

To complete this intervention, two VRBT exergames were chosen based on the Leutwyler and Hubbard (2012) and Sampaio, Subramaniam, Arena, and Bhatt (2016) studies. The warm-up phase and the beginning of the conditioning phase was completed using the "Just Dance 2015" game, whereby the volunteers reproduced the choreographies according to the songs. These games were reproduced using a multimedia projector (Epson Power Life, H309A, China) coupled to a console (Xbox One Kinect™, Microsoft, Redmond, WA, USA). The game was projected onto a white wall. The conditioning phase was commenced using the exercise game, called "Shape Up", whereby volunteers perform exercises by following a virtual personal trainer. Both games generate simulations of virtual environments with which volunteers interact using their own movements that are recorded using photographic or video motion capture equipment. The warm-up game intended to progressively increase HR, while the conditioning phase games were designed to maintain the volunteer's effort within the pre-set intensity and hence ensure the sessions safety in an identical way to the CR. The sequence of the games used in the experiment was defined in a pilot protocol.

Besides, during the routine of the VRBT session there were pauses between games that persisted for approximately 20 seconds, which triggered a reduction in the effort intensity. Yet, to minimize the effects of this reduction, at intervals, exercises were directed by a physiotherapist. These exercises were achieved by one series of 15 repetitions, in following sequence: foot flexion with elbow flexion, unilateral hip extension with opposite shoulder flexion and squat with arm abduction.

Primary outcome

The volunteers were told, beforehand, to avoid consumption of ANS stimulating ingredients such as coffee, tea, caffeinated beverages or chocolate, during the 24 hours prior to the evaluation.

Autonomic modulation was measured by HRV and logged during the session (Figure 2). Datasets were analyzed as follows: In the initial rest (Rep), HRV analyzes were performed from the 5th to the 10th minute; In the conditioning phase, HRV analyzes were performed every 5 min from the 5th to the 25th minute (Ex1 to Ex4). These four periods were evaluated via 256 intervals between consecutive heart beats (RR intervals) since the activities proposed by the games persisted for an average of 4 min. During the recovery period, HRV analyzes were performed every 5 min from the 1st to the 30th minute (Rec1 to Rec6). It is prominent that the initial and final 5 min of the conditioning phase were rejected from the analysis, since the games had a short time interval, an approximate mean of 3 min, which prevented the selection of time-series with at least 256 beats. This was assessed in the 1st and 12th weeks of training.

 # INSERT FIGURE 2 #

For HRV analysis, the beat-by-beat recording was obtained at a sampling rate of 1 kHz at the instants described above. Chronologically, these datasets were digitally filtered using standard filter Polar Precision Performance software (Polar Electro, Finland) (Kiviniemi, Hautala, Kinnunen, and Tulppo, 2007), with a moderate filter (median protection zone of six heart beats). Next, were perfected by manual filtering completed in Excel software (Microsoft Excel, 2010, USA), with a visual inspection of the temporal series of RR intervals, to eliminate premature ectopic beats and artifacts. Only series with at least 95% of sinus beats were included in the study (Godoy, Takakura, and Correa, 2005; Vanderlei *et al*, 2009; Catai *et al*, 2020). Afterwards, the data was transferred to the Kubios® HRV software (Bio-signal Analysis and Medical Image Group, Department of Physics, University of Kuopio, Finland) to calculate the HRV linear indexes (Tarvainen *et al*, 2014).

Regarding the linear indexes, the time domain analysis, was achieved by calculating rMSSD (root-mean square of differences between adjacent normal RR intervals in a time interval expressed in milliseconds) and SDNN (standard deviation of all normal RR intervals expressed in milliseconds). In the frequency domain, analysis was performed by computing spectral components of low (LF: 0.04 to 0.15 Hz) and high (HF: 0.15 to 0.40 Hz) frequency, in milliseconds (ms^2) and normalized units (nu). The spectral analysis was computed using the Fast-Fourier transform (FFT) (Vanderlei *et al*, 2009).

Statistical analysis

The sample for the present study was calculated based on the results of a pilot study. For this, we applied the mean standard deviation in the resting period of RMSSD index (10.37 ms) that presents the highest variability. Therefore, a magnitude difference of 10%, alpha risk of 5% and a sampling power of 80% were considered, with the final sample number being 17 individuals (exercise and recovery). The sample size was calculated online, via software located in http: //leedante.br.

The data analysis was performed blindly, the population profile was estimated by descriptive statistics and the results were expressed as mean and standard deviations in absolute and percentage numbers.

To analyze data, primarily the homogeneity was evaluated using the Mauchly Sphericity Test. If sphericity was violated, the Greenhouse-Geisser correction was enforced. To identify interactions between moments (Rep, Ex1 to Ex4, Rec1 to Rec6), two-way analysis of variance (ANOVA2) was required. Then, in order to demonstrate differences between moments, one-way analysis of variance (ANOVA1) was applied followed by Bonferroni post-test or, Friedmann test followed by Dunn's post-test. Statistical significance was set at 5% and computations completed via IBM SPSS Statistics v. 22.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Sample characterization

The patient's distribution throughout this study is illustrated in Figure 3. Briefly 43 individuals were initially assessed for eligibility and of these 12 were excluded. The 31 patients who participated in the study were randomized in clusters to perform the experimental procedures. The cluster allocation occurred according to the number of patients that could be accommodated in VRBT sessions (two patients per session). Regardless of when they completed the experimental procedures, every person randomly performed one CR session and one VRBT session before and after 12 weeks of VRBT with CR. As the experiments were split into two parts: exercise analysis and recovery analysis, after CR and VRBT sessions for evaluation of acute autonomic modulation, patients who did not perform the protocols (n = 2) and those who presented less than 95% of sinus beats in exercise (n = 4) or recovery (n = 1) were excluded. So, in the first week 25 patients in exercise and 28 in recovery were analyzed. After this, patients were submitted to 12 weeks of VRBT with CR for three times a week, with, two sessions of CR and one session of VRBT. To complete the program three patients gave-up and were excluded and, the remainder randomly performed a VRBT and another CR session to investigate the acute autonomic impact after the training. Of the patients that were evaluated during the second evaluation one was excluded from exercise analysis and two of recovery analysis. So, the 12th week sample of was composed of 21 patients in exercise analysis and 23 in recovery analysis. Sample description is revealed in Table 1. Losses were designated according to exercise and recovery periods.

 # INSERT FIGURE 3 #

 # INSERT TABLE 1 #

First week

The HRV index performance during the initial rest and conditioning is illustrated in Figure 4. It is imperative to realize that for the rMSSD index, the moments from Ex1 to Ex4 of both interventions were different regarding initial rest, but there was no difference between the groups. Concerning the SDNN index, it exhibited a progressive reduction to VRBT with a significant difference at time Ex4, while CR displayed intense and continuous reductions and with significant change for initial rest. Similarly, there were substantial differences between the groups in the moments Ex1 and Ex3, reassembling in Ex4. The LFnu and HFnu indices at all times presented significant differences in relation to rest for VRBT and significant differences between groups at Ex1, Ex3 and Ex4. Taking into consideration the $HFms^2$ index, for the CR there was a significant change between all the exercise moments and the resting stage, whilst for the VRBT there was only a significant difference at the Ex3 and Ex4 moments. Yet, there was a significant alteration between the groups at time Ex4. For the $LFms^2$, there were no changes between the groups, but the moments Ex3 to Ex4 revealed significant modifications regarding resting for VRBT.

The HRV index behavior during the initial rest and in the recovering is illustrated in Figure 5. There were no important changes to rMSSD, $LFms^2$ and $HFms^2$ indexes. The SDNN, HFnu, LFnu indexes revealed significant differences in Rec1 with regards recovering in both interventions.

 # INSERT FIGURES 4 AND 5 #

<u>Twelfth week</u>

The HRV index behavior in the twelfth week to the initial rest and conditioning moments is illustrated in Figure 6. For the rMSSD and $HFms^2$ indexes, the moments from Ex1 to Ex4 of both interventions were different for initial rest and there was no difference between the groups. Regarding the SDNN index, it exhibited significant differences between the groups in all moments with higher values for VRBT. Evaluation between moments, the CR exhibited significant difference for all moments, whilst for VRBT there is a significant difference between Ex2 to Ex4. For initial rest, the LFnu and HFnu indexes reveal significant difference in Ex1 and Ex2 moments to VRBT; in Ex1 moment to CR and significant difference between groups in Ex1 and Ex3 moments. In LFms² index, Ex2 to Ex4 moments show significant differences on initial rest to VRBT and CR and significant change between groups in the Ex3 moment.

The HRV index behavior during the initial rest and in recovering in the twelfth week is illustrated in Figure 7. There were no significant changes to rMSSD, LFnu, HFnu and HFms² indexes. The SDNN indexes displayed significant difference in Rec1 concerning recovery in both interventions. For LFms² indexes, there are significant changes for initial rest in Rec5 and Rec6 in CR.

 # INSERT FIGURES 6 AND 7 #

Comparison VRBT (First & Twelfth week)

The contrast of the HRV indexes behavior of HRV during the initial rest and exercise of the 1st versus the 12th week are presented in Figure 8. For the rMSSD and HFms² index, the moments from Ex1 to Ex4 of both interventions were changed for rest. The SDNN index presented significant differences at Ex4 at rest during the 1st week. In the 12th week, the moments from Ex2 to Ex4 uncovered significant changes at rest. The LFnu and HFnu indices exhibited significant changes at rest always of the 1st week and at the Ex1 and Ex2 moments of the 12th week. None presented alterations between the groups. For the LFms² index, the moments of Ex3 and Ex4 displayed significant differences for rest in the 1st week, whilst in the 12th week, there were significant differences in the moments of Ex2 to Ex4.

Figure 9 illustrates in absolute numbers and standard deviation, the comparison of HRV indexes behavior during the initial rest and recovery period of the 1st versus the 12th week. No significant differences were achieved for the rMSSD, LFms² and HFms² indices. The SDNN index exhibited a significant difference in relation to rest in Rec1 in both interventions and there was no change between the groups. The LFnu and HFnu indices presented significant difference in relation to rest in Rec1, only in the 1st week and there was no change between the groups. There were no adverse events during the protocol.

 # INSERT FIGURES 8 AND 9 #

DISCUSSION

To our knowledge, this is the first study to investigate acute cardiac autonomic modulation impact during and after VRBT sessions and compare with the responses obtained in a session of conventional Cardiovascular rehabilitation CR in patients with CD or associated risk factors.

The results around the first week demonstrate that the acute response pattern of autonomic modulation during and after both therapies were physiological and similar, yet, the magnitude of the response was greater in VRBT than CR for volunteers with CD or with RF. During the VRBT training, greater vagal withdrawal was observed (HFnu) and greater sympathetic stimulation (LFnu). Likewise, there was a progressive lessening in overall HRV, which only resembled CR in the last 5 min (SDNN), and a reduction in the rMSSD index values, but then without modifications between therapies. Regarding recovery, global HRV (SDNN), parasympathetic (HFnu) and sympathetic modulation (LFnu) was restored from the 5th min in both therapies.

Physiologically, the initiation of exercise up to 3rd min typically corresponds to the initial reaction period to exercise (Fisher, Young, and Fadel, 2015) where there is a surge in HR (Selye, 1936) which varies steadily with the intensity of the exercise, besides: individual biological characteristics, perception of effort and previous experiences of the individual.

When evaluating autonomic modulation in this period, it is detected that the main influence for this variation is parasympathetic inhibition, which can be demonstrated by the significant decrease in RMSSD and HFnu indexes. Besides, the greater the sympathetic stimulation (LFnu) that is expected, so it is that the sympathetic nervous system (SNS) impacts the immediate increase in HR (Takahashi *et al*, 2007).

During prolonged submaximal aerobic exercise, the body adapts to the condition and the HRV indexes fluctuate only slightly (Selye, 1936). This can be observed by slight variation in the behavior of HRV indexes found in conventional CR. But, the results obtained in the VRBT for the SDNN index indicate a gradual reduction. This could be related to the characteristic of the VRBT, as during its performance there were pauses between games.

In the recovery period, HRV returned to the pre-exercise conditions, and this recovery is typically credited to the restoration of the parasympathetic nervous system (PNS) and, secondarily, to the reduction of SNS hyperactivity (Fisher, Young, and Fadel, 2015). These similar results were observed in this study, since CR and VRBT restored PNS from the 5th min onwards, given the significant difference in HFnu index in Ex1 in Figure 5.

The higher values of autonomic modulation responses in VRBT when compared to CR may pose some questions: 1) It was the first time that individuals performing VRBT, which may have produced larger exercise intensity and greater emotional stimulation, as when submitted to a new situation the individual may present a greater stimulation of the SNS (Fisher, Young, and Fadel, 2015). This factor did not occur for CR, considering the previous practice of exercise on a treadmill; 2) The accomplishment of more complex movements in the VRBT, once the volunteers had performed familiarization; 3) Performing VRBT in pairs; this may have stimulated rivalry amongst some volunteers. This may not have occurred with conventional RC.

Another intention of this study was to evaluate after a 12-week cardiovascular rehabilitation program involving two CR sessions and one using virtual reality, the acute responses on autonomic modulation during and after the VRBT session would be different from those obtained with those of a CR session and with those obtained in the first session of VRBT. Overall, the results confirm that again the acute response pattern of autonomic modulation during and after the therapies were physiological and similar.

During the VRBT practice, the LFnu and HFnu indexes did not present significant changes in Ex3 and Ex4 moments in relation to the Rep as in the 1st session, indicating that an adaptation during the conditioning phase. Similarly, it was detected that after twelve weeks of practice, the global HRV (SDNN index) displayed responses more closely resembling the pattern obtained in CR. This alteration can be vindicated by the volunteers learning the techniques for performing the commands and movements and thus better execution. These results were similar to those of sedentary adults, since Santana *et al*. (2016) found similar BP and HR behaviors during VRBT in comparison to classic aerobic exercise on an exercise bike.

Regarding recovery of VRBT session, the global HRV (SDNN index) was restored from the 5th min in 1st session and 12th sessions, but the parasympathetic and sympathetic modulation, given by the HFnu and LFnu indexes, were restored before the 5th min only in the 12th session; suggesting adaptation.

Nonetheless, to our knowledge there are no similar studies evaluating the acute responses of autonomic modulation induced by VRBT simulation in patients with CD or RF. This, the first study to address this concern.

Too, this study is of clinical importance in providing evidence concerning a new technique that is being made available in the physical therapy labor market and that needs to be investigated to ensure the safety of the practice of VRBT by cardiac patients. The use of virtual reality as an alternate modality of CR is a possibility and may have potential benefits such as greater motivation and patients' adherence in treatment. But it needs to be investigated to ensure the efficiency and safety of patients.

Despite the advantages cited above; this study had some limitations. Firstly, the VRBT training protocol was achieved using the “Just Dance 2015” and “Shape Up” games. These games are commercial and were designed for entertainment purposes, not specifically for treatment of DC or RF; and this makes it problematic to define intensity and load adjustments. Likewise, during the conditioning phase for the VRBT, the activities proposed by the games persisted for an average of 4 min. So, between the exchange of games, there was an interval with reduced effort intensity. Yet, to minimize the effects of this intensity reduction, at intervals, exercises were completed whilst guided by a therapist. Though, this was unable to prevent the evaluation of the results, since the analysis of the 5 min at the beginning and end of the exercise were discarded and the effects on autonomic modulation during and after the therapies were observed.

CONCLUSIONS

We concluded that, in the 1st week, the acute impacts on autonomic modulation during therapies was comparable, yet, the magnitudes were higher in VRBT than in CR. Concerning the recovery, overall HRV is restored from 5 min with both therapies, and PNS from 15 min on CR alone, while 30 min was insufficient for recovery on VRBT. After 12 weeks of training associating VRBT with CR, the acute response pattern of autonomic modulation during and after therapy was physiological, comparable and demonstrates an adaptation with benefits for patients with CD or RF.

NOTES

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding: The present study was developed under grant support from the Foundation for Research Support of the State of São Paulo (FAPESP) 2018/18276-6 and National Council for Scientific and Technological (CNPq) – Financing Code and 46124.

Authors' contributions: **Paula F. Silva and Ana Laura Ricci-Vitor** participated since the conception and design of the work; participated in the acquisition, analysis, interpretation of data for the work; participated yet in the drafting of the work and revising it critically for important intellectual content; **Mayara M. A. Cruz and Giovanna L. B. Borges:** participated in the acquisition and interpretation of data, participated yet in drafting the work and revising it critically for important intellectual content; **David M. Garner:** participated in interpretation of data, in the drafting the work and revising it critically for important intellectual content; and **Luiz C. M. Vanderlei:** participated since the conception and design of the work; participated in analysis and interpretation of data, participated yet in the drafting the work and revising it critically for important intellectual content. All authors participated in the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Congresses: The partial version of this paper was presented in two local events in 2018 and the final version was presented in two local events and in one national conference in 2019.

Acknowledgements: The authors would like to thank the Laboratory of Stress Physiology and Laboratory of the Faculty of São Paulo State University (UNESP), School of Technology and Sciences, Presidente Prudente, for all assistance during this work.

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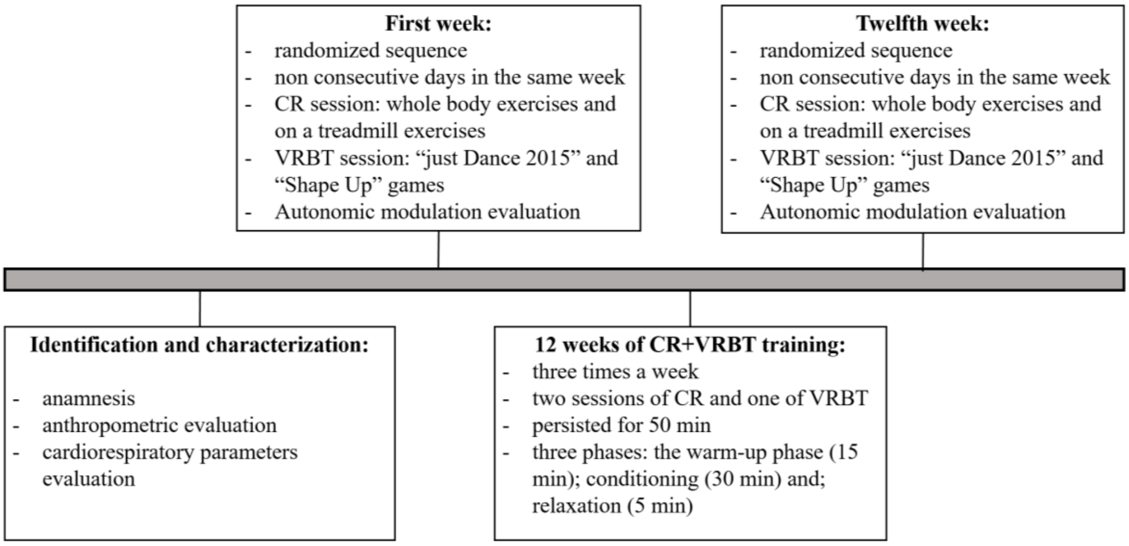
TABLE

Table 1. Characterization of the patients

Characterization		(n = 28)	
Age (years)		63.39 ± 12.48	
BMI (kg/m²)		29.34 ± 4.61	
Gender			
	Female	n = 14	50.00%
	Male	n = 14	50.00%
Diagnosis			
	CD	n = 20	71.40%
	RF	n = 8	28.60%
Comorbidities			
	Yes	n = 19	67.86%
	No	n = 9	32.10%
Signs and symptoms			
	Yes	n = 11	39.30%
	No	n = 17	60.70%
Risk factors			
	Diabetes mellitus	n = 12	42.90%
	Dyslipidemia	n = 13	46.40%
	Hypertension	n = 18	64.30%
	Family history	n = 13	46.40%
	Obesity	n = 9	32.10%
	Smoking	n = 2	7.10%
Pharmacotherapies			
	Aldosterone antagonist	n = 5	17.90%
	Platelet antiaggregating	n = 17	60.71%
	Antiarrhythmic	n = 2	7.10%
	Coronary vasodilator	n = 3	10.70%
	Beta blocker	n = 20	71.40%
	Ca^+ channel blockers	n = 5	17.90%
	Diuretic	n = 10	35.70%
	ACE inhibitor	n = 17	60.70%
	Statins	n = 15	53.60%
	Hypoglycemic	n = 7	25.00%
	Vasodilator	n = 3	10.70%
Cardiorespiratory parameters			
	Heart rate (bpm)	73.00 ± 7.73	
	Systolic blood pressure (mmHg)	118.93 ± 13.97	
	Diastolic blood pressure (mmHg)	71.07 ± 8.32	
	Respiratory rate (rpm)	16.93 ± 4.49	
	Peripheral oxygen saturation (%)	96.32 ± 1.47	

Legend: n: number; BMI: body mass index; kg: kilograms; m: meters; CD: cardiovascular diseases; RF: risk factors; kg: kilograms; m²: squared meters; Ca^+: calcium; ACE: angiotensin II converting enzyme; bpm: beats per minute; mmHg: millimeters of mercury; rpm: respiratory incursions per minute. The results are expressed as mean and standard deviation or as a percentage and absolute number.

Figure 1. Design of the study.



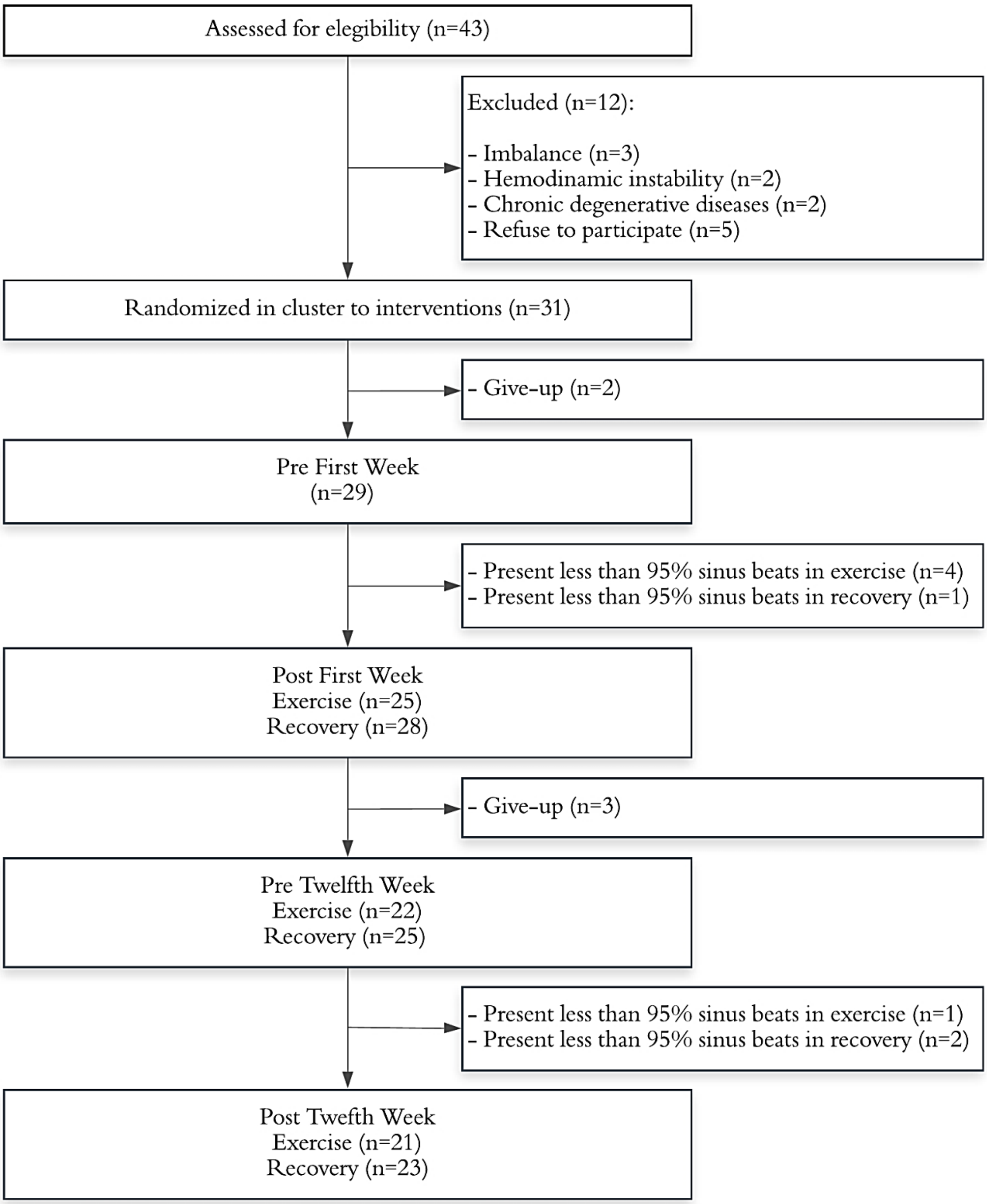
Legend: CR: Cardiovascular Rehabilitation; VRBT: Virtual Reality-Based Therapy; min: minutes.

Figure 2. Measurement of autonomic modulation during the session.

0th to 5th	5th to 10th	0th to 5th	5th to 10th	10th to 15th	0th to 5th	5th to 10th	10th to 15th	15th to 20th	20th to 25th	25th to 30th	0th to 5th	5th to 10th	10th to 15th	15th to 20th	20th to 25th	25th to 30th
Initial rest 10 min		**Warm-up 15 min**			**Conditioning* 30 min**						**Recovery 30 min**					

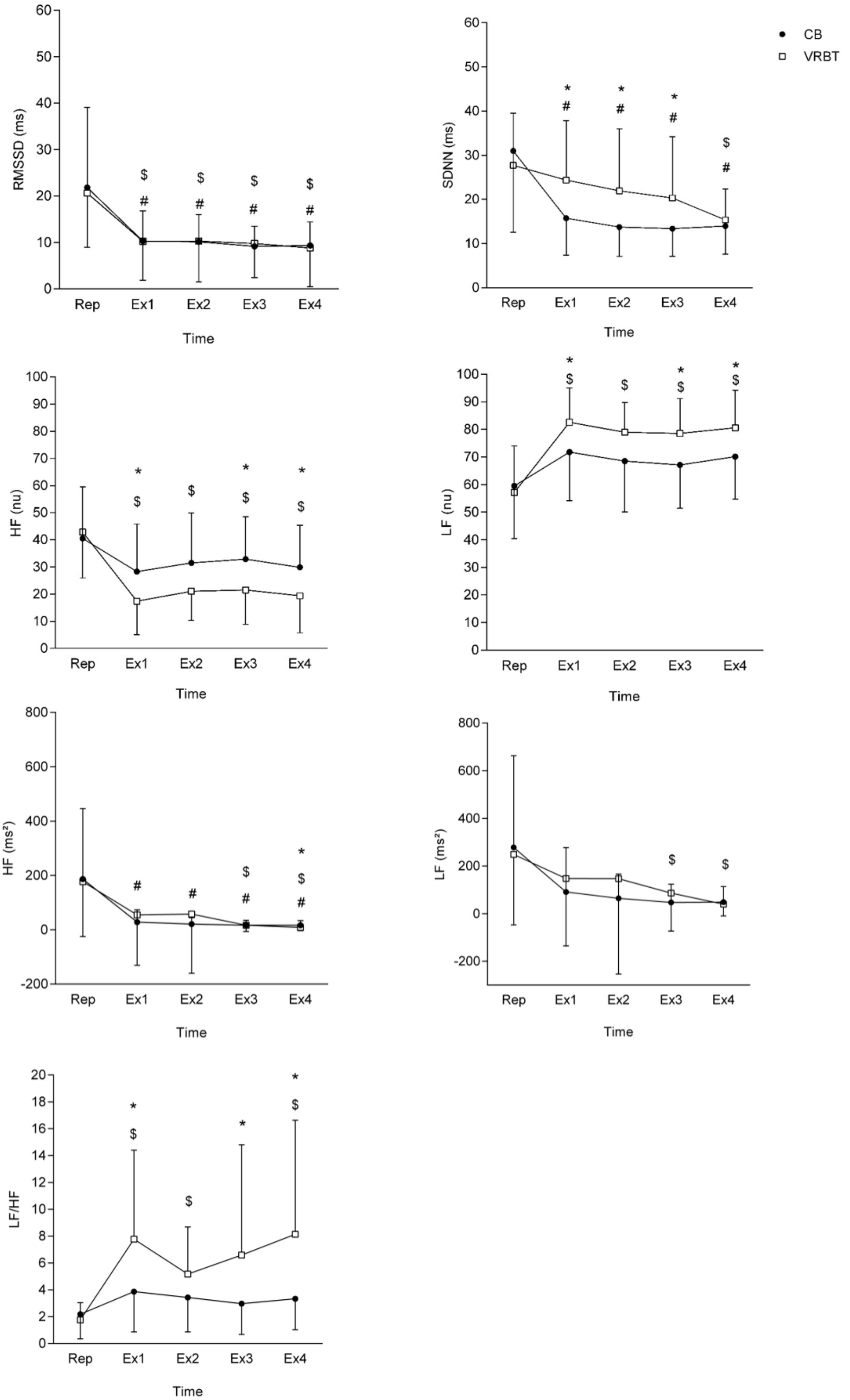
Legend: CR: Cardiovascular Rehabilitation; VRBT: Virtual Reality-Based Therapy; n: number.

Figure 3. Flowchart of volunteer losses.



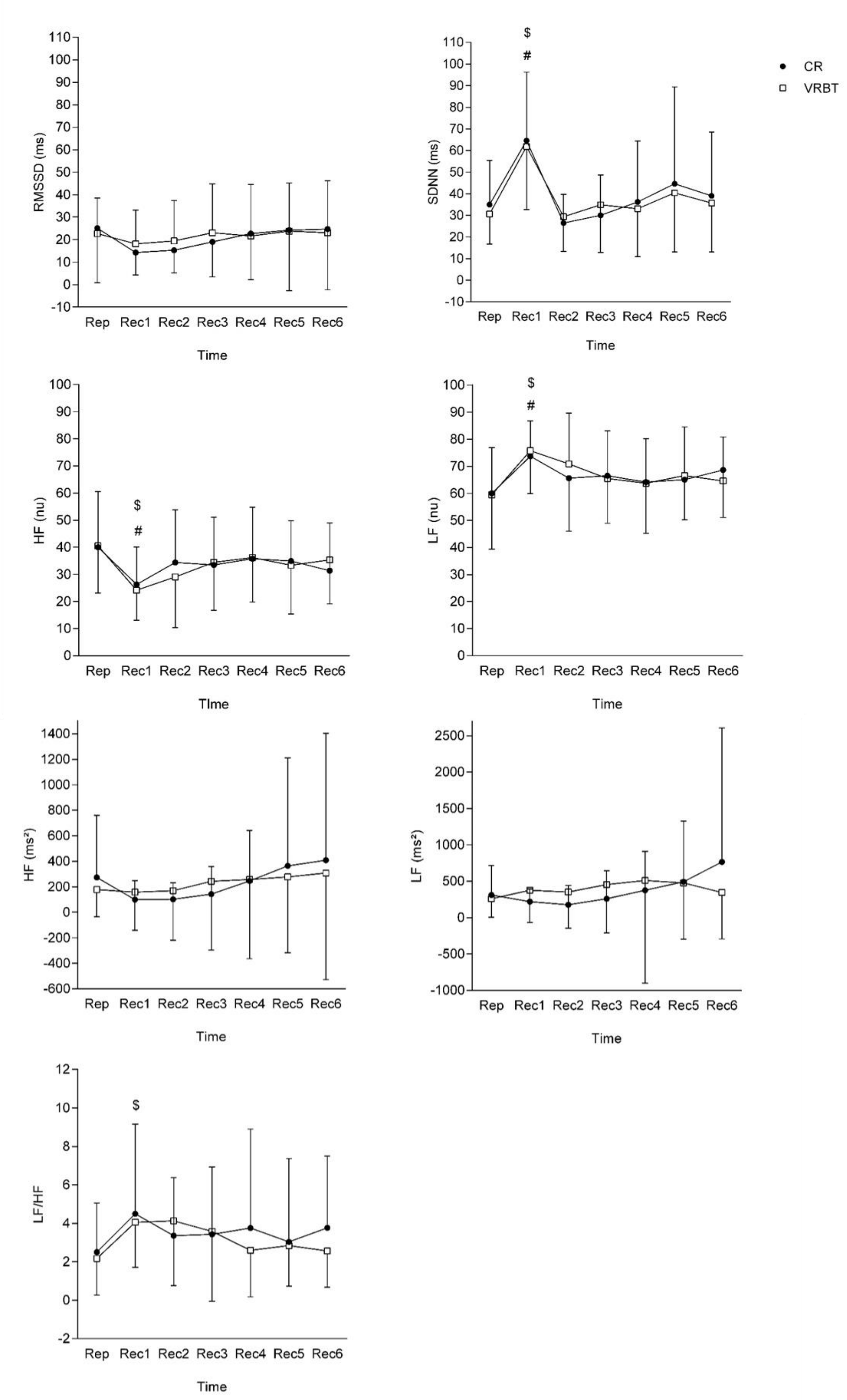
Legend: CR: Cardiovascular Rehabilitation; VRBT: Virtual Reality-Based Therapy; n: number.

Figure 4. The behavior of HRV indexes before and during interventions.



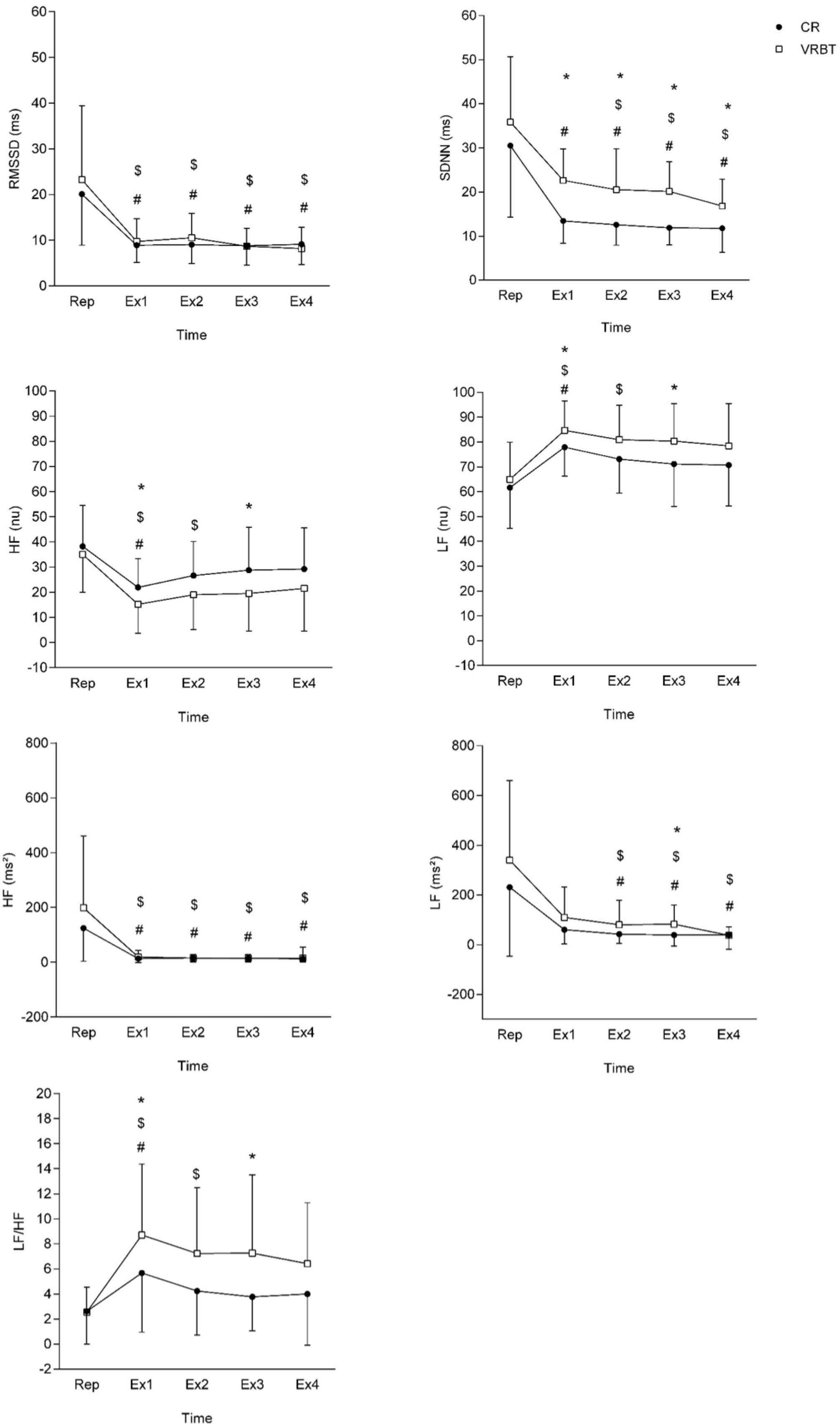
Legend: VRBT: Virtual Reality-Based Therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Ex1: 5^{th} to 10^{th} min to exercise; Ex2: 10^{th} to 15^{th} min of exercise; Ex3: 15^{th} to 20^{th} min of exercise; Ex4: 20^{th} to 25^{th} min of exercise; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; $p<0.05$); $^{\#}$Difference compared Ex in relation to Rep in CR (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$) $^{\$}$ Difference compared Ex in relation to Rep in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$).

Figure 5. The behavior of HRV indexes before and after the interventions.



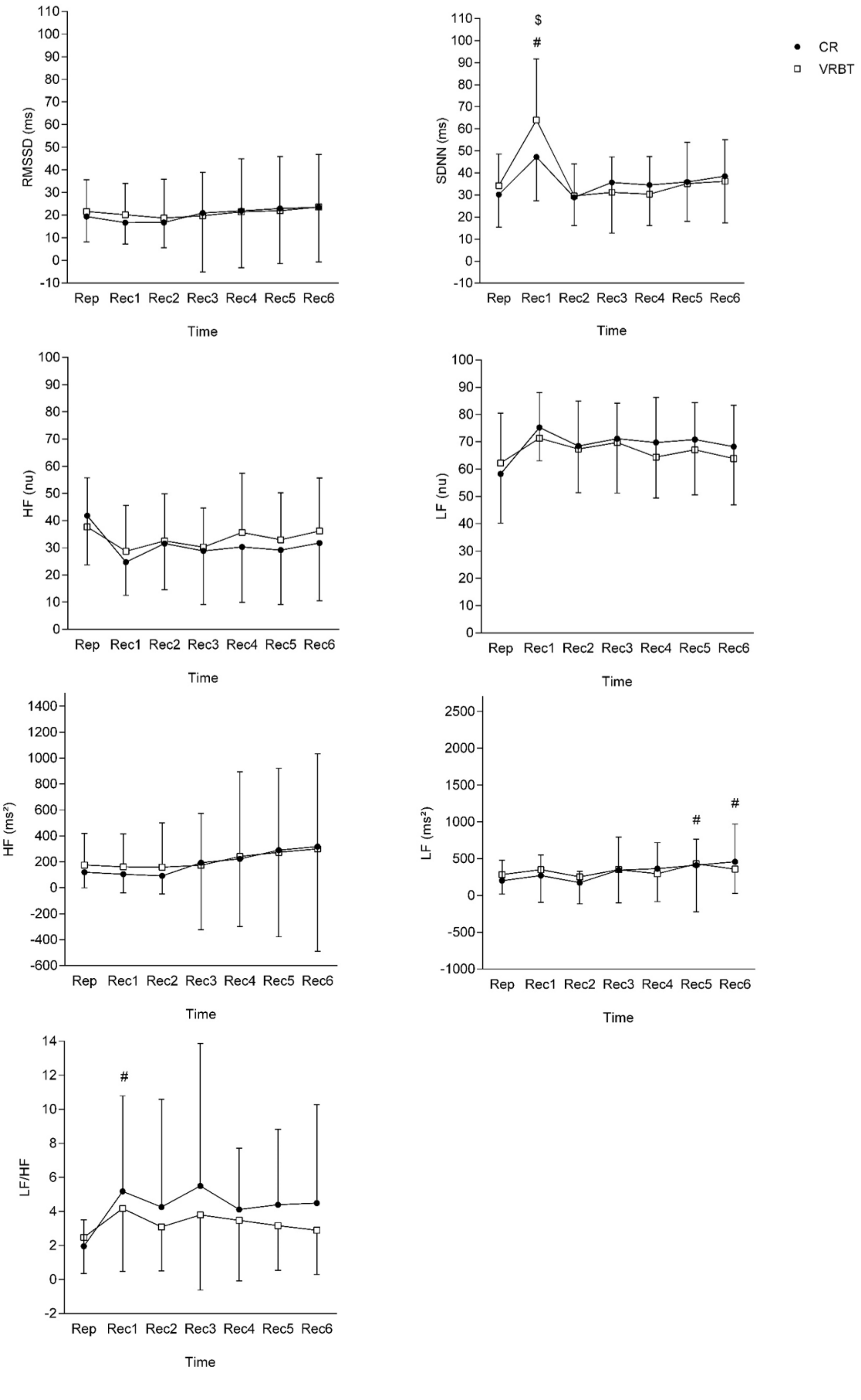
Legend: VRBT: Virtual reality-based therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Rec1: 0 to 5th min of recovery; Rec2: 5th to 10th min of recovery; Rec3: 10th to 15th min of recovery; Rec4: 15th to 20th min of recovery; Rec5: 20th to 25th min of recovery; Rec6: 25th to 30th min of recovery; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; $p<0.05$); $^{\#}$Difference compared Ex in relation to Rep in CR (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$) $^{\$}$ Difference compared Ex in relation to Rep in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$).

Figure 6. The behavior of HRV indexes before and during interventions in the twelfth week.



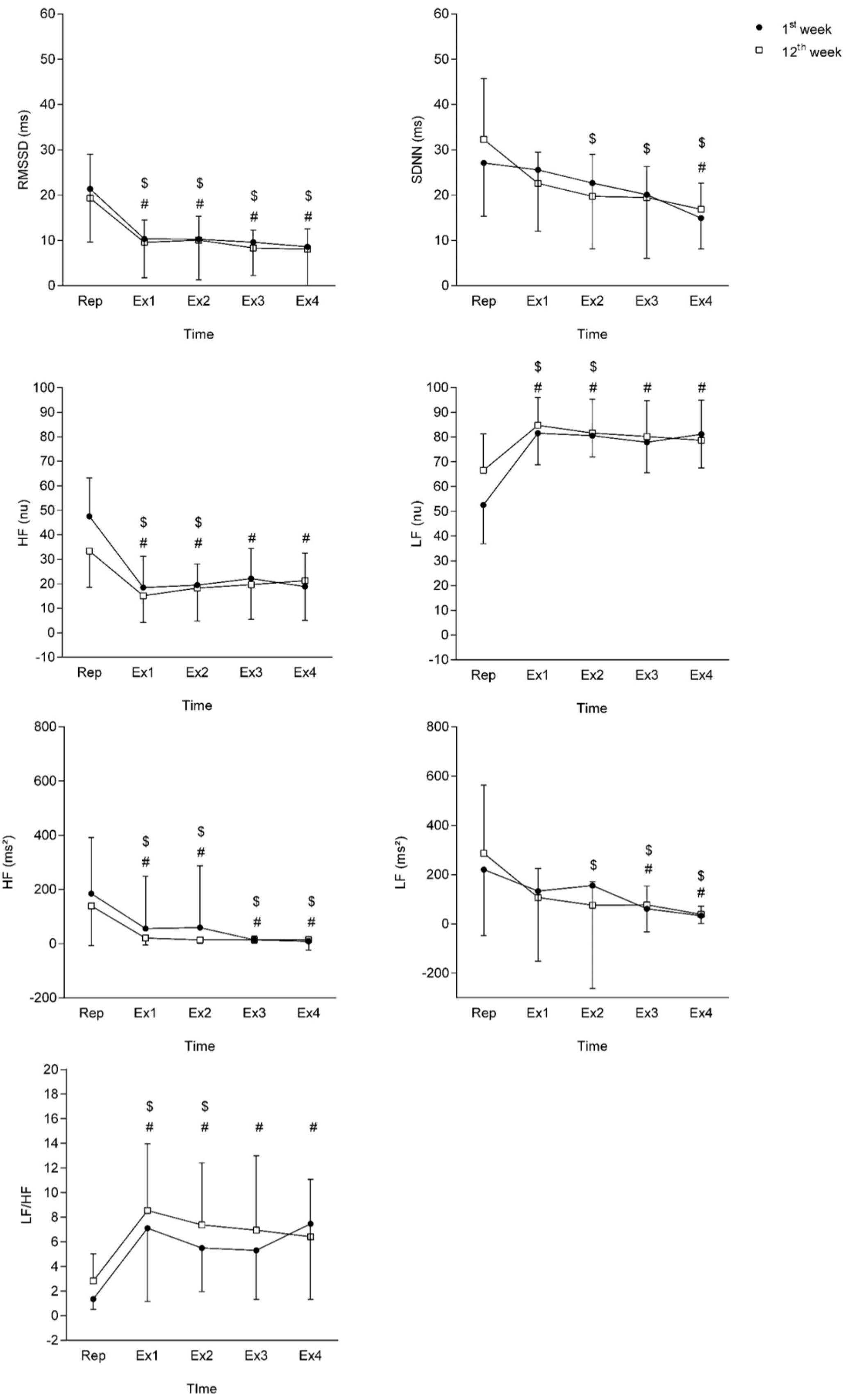
Legend: VRBT: Virtual Reality-Based Therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Ex1: 5^{th} to 10^{th} min to exercise; Ex2: 10^{th} to 15^{th} min of exercise; Ex3: 15^{th} to 20^{th} min of exercise; Ex4: 20^{th} to 25^{th} min of exercise; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; $p<0.05$); $^{\#}$Difference compared Ex in relation to Rep in CR (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$) $^{\$}$ Difference compared Ex in relation to Rep in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$).

Figure 7. The behavior of HRV indexes before and after the interventions in twelfth week.



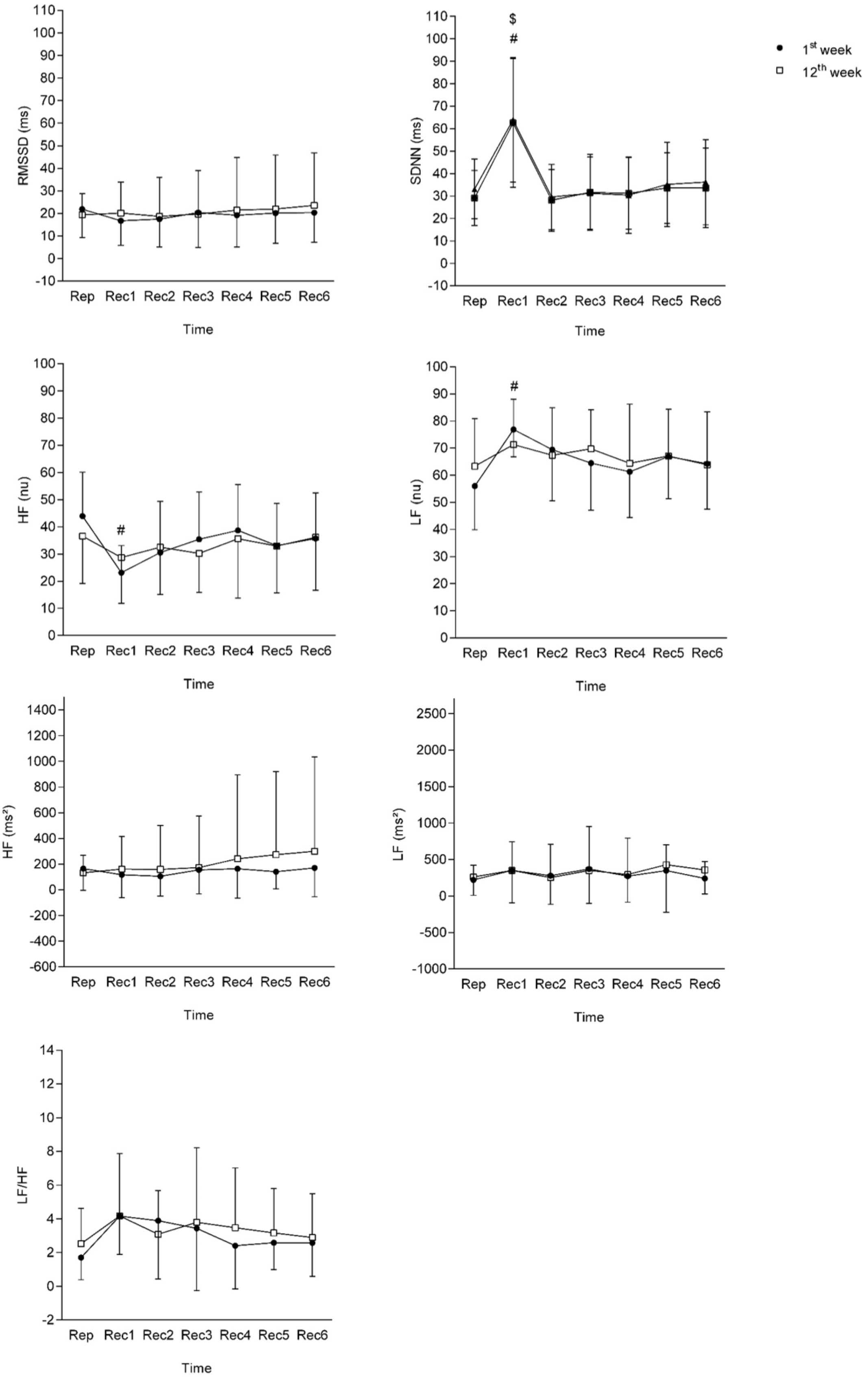
Legend: VRBT: Virtual Reality-Based Therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Rec1: 0 to 5th min of recovery; Rec2: 5th to 10th min of recovery; Rec3: 10th to 15th min of recovery; Rec4: 15th to 20th min of recovery; Rec5: 20th to 25th min of recovery; Rec6: 25th to 30th min of recovery; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; p<0.05); #Difference compared Ex in relation to Rep in CR (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; p<0.05) $ Difference compared Ex in relation to Rep in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; p<0.05).

Figure 8. The behavior of HRV indexes before and during the first and twelfth in VRBT session.



Legend: VRBT: Virtual Reality-Based Therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Ex1: 5^{th} to 10^{th} min to exercise; Ex2: 10^{th} to 15^{th} min of exercise; Ex3: 15^{th} to 20^{th} min of exercise; Ex4: 20^{th} to 25^{th} min of exercise; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; $p<0.05$); $^{\#}$Difference compared Ex in relation to Rep in first week in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$) $^{\$}$ Difference compared Ex in relation to Rep in twelfth week in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; $p<0.05$).

Figure 9. The behavior of HRV indexes before and after the first and twelfth in VRBT session.



Legend: VRBT: Virtual Reality-Based Therapy; CR: cardiovascular rehabilitation; rMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval expressed; SDNN: standard deviation of all normal RR intervals; LF: low frequency; HF: right frequency; Rep: 5^{th} to 10^{th} min of initial rest; Rec1: 0 to 5^{th} min of recovery; Rec2: 5^{th} to 10^{th} min of recovery; Rec3: 10^{th} to 15^{th} min of recovery; Rec4: 15^{th} to 20^{th} min of recovery; Rec5: 20^{th} to 25^{th} min of recovery; Rec6: 25^{th} to 30^{th} min of recovery; Values expressed in mean and standard deviation. *Difference between interventions (Mann-Whitney test; p<0.05); $^{\#}$Difference compared Ex in relation to Rep in first week in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; p<0.05) $^{\$}$ Difference compared Rec in relation to Rep in twelfth week in VRBT (One-way ANOVA followed by Bonferroni post-test or Friedmann test followed by Dunn's post-test; p<0.05).