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ORIGINAL REPORT

LEFT-VENTRICULAR FUNCTION AND AUTONOMIC CARDIAC ADAPTATIONS AFTER SHORT-TERM INPATIENT CARDIAC REHABILITATION: A PROSPECTIVE CLINICAL TRIAL

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Objective: **Cardiac rehabilitation is associated with cardiac autonomic and physiological benefits. However, it is unclear whether baseline left ventricular function (LVF) impacts on training-induced cardiac autonomic adaptations. The aim of this study was to assess the cardiac autonomic adaptations in patients with varying left ventricular function profiles undergoing coronary artery bypass grafting and cardiac rehabilitation.**

Design: **Assessor-blinded prospective trial.**

Patients: **Forty-four patients undergoing coronary artery bypass grafting, divided into normal LVFN (≥55%, $n=23$) or reduced LVFR (35–54%, $n=21$) were evaluated.**

Method: **Cardiac autonomic function was evaluated by heart rate variability indexes obtained both pre- and post-cardiac rehabilitation. All patients participated in a short-term (approximately 5 days) supervised inpatient physiotherapy program.**

Results: **There were differences in heart rate variability indexes, correlation dimension and SD2 according to time and group (e.g. interaction time (effect of cardiac rehabilitation) vs group (LVFN vs LVFR), $p=0.04$). Simple main effects analysis showed that the LVFR group benefited to a greater degree from cardiac rehabilitation compared with the LVFN group. Heart rate variability indexes increased significantly in the former group compared with the latter.**

Conclusion: **Among post-coronary artery bypass grafting patients engaged in short-term inpatient rehabilitation, those with reduced left ventricular function are most likely to have better cardiac autonomic adaptations to exercise-based rehabilitation.**

Key words: coronary artery bypass grafting; physiotherapy; exercise therapy; autonomic nervous system; heart rate control.

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INTRODUCTION

Heart rate variability (HRV) is the most frequently used non-invasive method for assessing autonomic activity and its influence on the cardiovascular system. Thus, HRV is valuable in providing information on the heart's ability to respond to normal regulatory impulses that affect its rhythm (1). It is well known that after cardiac procedures such as cardiac valve surgery and coronary artery bypass grafting (CABG), HRV becomes significantly decreased (2, 3).

Decreased HRV is associated with abnormal and insufficient adaptability of the autonomic nervous system and has been shown to be a predictor of hemodynamic instability and mortality (1). In this context, compromised cardiac autonomic (CA) regulation may result in increased arrhythmia susceptibility and subsequent risk of cardiovascular death, more myocardial ischemic episodes and worsening clinical course after CABG with more inotropic support and longer periods in the intensive care unit (4–6).

For these reasons, many investigators have focused on strategies positively impacting the CA system in patients undergoing cardiac surgery, one of which is exercise-based cardiac rehabilitation (CR) (7, 8). In previous studies, long-term outpatient CR was associated with favorable alterations in HRV potentially resulting from adaptations in peripheral and central neural pathways (9).

Recently, however, our group has demonstrated that a short-term inpatient CR program results in early CA benefits in post-CABG patients (10). However, the influence of key baseline characteristics on the impact of CA alterations following CR, such as left ventricular function (LVF), was not considered.

A previous study (11) assessing physical performance reported that patients with poor LVF are most likely to respond favorably to inpatient CR. In addition, it is known that these patients are more likely to demonstrate impaired CA function, characterized by lower values of HRV (12). In this context, little information exists on how normal vs reduced LVF affects CA adaptations after inpatient CR in post-CABG patients.

The aim of this study was to assess the CA adaptations in patients with normal and reduced LVF undergoing CABG and

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subsequently a short-term CR program. Hence, our primary research question was: Is an inpatient exercise-based program after CABG more effective in patients with reduced LVF compared with those with normal LVF with respect to improving CA activity? The hypothesis of this study was that patients with reduced LVF are likely to derive the greatest benefit in CA activity following CR.

METHODS

Design

An assessor-blinded prospective trial was conducted within the Coronary Care Unit and Cardiovascular Ward of Santa Casa Araraquara Hospital following approval by the Human Research Ethics Committee (197/2005). Patients awaiting first-time CABG were invited to participate in the study, and enrolled after giving written informed consent. Participants were divided into groups according to left ventricular ejection fraction (LVEF) assessed by echocardiography (Teichholz method). Grouping consisted of: (*i*) LVF normal group (LVFN group) composed of patients with a LVEF ≥ 55%; or (*ii*) LVF reduced group (LVFR group) composed of patients with a LVEF between 35–54% regarded as mild to moderate dysfunction secondary to ischemic etiology (13). The study was registered with ClinicalTrials.gov (ACTRN12610000559011).

Pre-operatively, the patient's age, gender, weight, height, body mass index (BMI), cardiac risk factors and other relevant medical history were documented. Additionally, a pulmonary function test was performed to investigate the presence of chronic obstructive pulmonary disease (COPD) and education about the effects of surgery on cardiorespiratory function, post-operative routines and the CR program were provided. Post-operatively, surgical and hospital data were recorded and all patients were engaged in CR supervised by 1 of 3 members of the physiotherapy staff, who were specifically trained to participate in this investigation.

The outcome measures of heart rate (HR) intervals between two consecutive cardiac beats (RR intervals) were collected both pre- and post-operatively. For this study, post-operative assessments were conducted on the first post-operative day, prior to initiation of CR, and follow-up assessments were performed after completion of CR, on the day of hospital discharge.

Participants

A total of 44 patients undergoing elective CABG surgery with cardiopulmonary bypass and with normal ($n = 23$) or reduced ($n = 21$) LVF were included in this study. Exclusion criteria were emergent or concomitant surgery, recent myocardial infarction (less than 6 months), implanted pacemaker, unstable angina, chronic disturbances in heart rhythm, significant acute arrhythmias, valvular heart disease, COPD, severe non-cardiac diseases, and the inability to perform CR according to our protocol.

Intervention

Short-term supervised inpatient physiotherapy exercise protocol. All patients participated in a once-daily supervised postoperative exercise protocol of early mobilization, which has been described previously (10) and detailed in Table I. The program was initiated on first post-operative day and continued until discharge. Estimated energy expenditure during this program was initially set at approximately 2 metabolic equivalents (METs) and progressed to 4 METs (14, 15). The HR during exercise was monitored and not allowed to exceed 20 bpm above the resting value, the HR monitoring system utilized was a Polar S810i telemetry system (Polar Electro Oy, Kempele, Finland), as described previously (15).

The patients performed voluntary deep-breathing exercises from functional residual capacity to total lung capacity (40 deep breaths in 4 sets of 10, each breath included a 5 s hold at the end of inspiration) followed by coughs or huffs (with wound support) supervised once daily, for approximately 15 min. Patients were also instructed to perform these breathing and coughing exercises independently every waking hour.

For daily patients monitoring, systolic (SBP) and diastolic blood pressures (DBP) were obtained indirectly, axillary body temperature was measured and the respiratory rate also was measured using VivoMetrics' LifeShirt System (VivoMetrics Inc, Ventura, USA). The patients were also asked to quantify their pain according to a 4-point verbal rating scale (VRS-4) (16).

Outcome measures

Primary outcome. The primary outcome measures were non-linear HRV indexes (approximate entropy, correlation dimension and SD2) after a short-term (approximately 5 days) inpatient supervised physiotherapy protocol. Previous studies have shown that these non-linear measures can detect abnormalities in CA regulation that may not be detected with traditional measures (17, 18).

Secondary outcome. As a secondary outcome measure we analysed HRV indexes in traditional time domain measures (mean of RR intervals (RR), square root of the mean squared differences of successive RR (rMSSD), standard deviation of RR (STD RR), baseline width of the RR histogram (TINN) and integral of the RR histogram divided by the height of the histogram (RR tri) index).

HR and RR interval (RRi) recording. The HR and RRi were recorded offline and continuously using a Polar S810i telemetry system for further analysis of HRV, at 3 time-points: (*i*) pre-operative (T0) for autonomic basal function characterization; (*ii*) first post-operative day (T1); and (*iii*) discharge (T2). At these time-points, T0, T1 and T2, the recording of HR and RRi were performed for 10 min in the afternoon in the sitting position at rest. Care was taken to avoid any manipulations in the patients during recording and no patient consumed caffeinated drinks/foods or smoked on the morning of assessments or during the procedure. Each patient rested for 10 min before the initiation of data collection to ensure the stabilization of HR.

Table I. *Short-term supervised inpatient physiotherapy protocol*

Step[a]	Physiotherapy exercise protocol description
Step 1	Active-assistive exercises of the lower/upper extremities – ankles and wrists, 5 sets of 10 repetitions; bed inclined at 45º. (Estimated energy cost = 2 METs, approximate time spent = 15 min).
Step 2	Active-assistive exercises of upper and lower limbs in sitting position (90º) – flexion-extension of the bilateral shoulder, elbow, wrist, knee and ankle; adduction-abduction of the hips (2 sets of 15 for each) and orthostatic position/walking on spot (5 min) as tolerated. (Estimated energy cost = 2–4 METs, approximate time spent = 40 min).
Step 3	Active exercises, as in step 2, but in 3 sets of 15 in the sitting position and ambulation within the inpatient ward (5 min). (Estimated energy cost = 3–4 METs, approximate time spent = 50 min).
Step 4	Exercises similar in step 3 in sitting position; ambulation within the inpatient ward (10 min). (Estimated energy cost = 3–4 METs, approximate time spent = 55 min).
Step 5	Exercises similar in step 3 in orthostatic position, ambulation (10 min) and flight of stairs (four steps). (Estimated energy cost = 3–4 METs, approximate time spent = 60 min).

[a]Each step corresponds to one day of postoperative intervention.
MET: metabolic equivalent.

HRV analysis. The HR data were transferred to the microcomputer and the RRi series were reviewed by visual inspection. Only segments with > 90.0% pure sinus beats were included in final analysis. The data were entered into Kubios HRV analysis software (MATLAB, version 2 beta, Kuopio, Finland) and HRV analysis proceeded with one series of 300 sequential RRi.

The non-linear properties of HRV were analysed using measures such as approximate entropy (ApEn) (19), correlation dimension (CD) (20) and Poincaré plot (21). ApEn quantifies the regularity of time series data and is represented as a simple index for the overall complexity and predictability of each time series. Large values of ApEn indicate high irregularity and smaller values of ApEn indicate a more regular signal. Thus, the highest ApEn value reflects better health and function (19).

The CD index represents a measure of the dimensionality of the space occupied by state vectors or the number of the degrees of freedom of a time series, also referred to as fractal dimension. A higher CD reflects more degrees of freedom of the cardiac pacemaker and, therefore, the greater the range of possible adaptive responses to internal or external stimuli in an ever-changing environment (20).

The non-linear analysis of the Poincaré plot of RRi was applied and the following two descriptors of the Poincaré plot were used in the study: SD1 – the standard deviation measuring the dispersion of points in the plot perpendicular to the line-of-identity. This parameter is usually interpreted as a measure of short-term HRV, which is caused mainly by respiratory sinus arrhythmia (parasympathetic modulation); and SD2 – the standard deviation measuring the dispersion of points along the identity line, which is interpreted as a measure of both short- and long-term HRV (overall HRV) (21).

Linear traditional measures in the time domain HRV analysis were evaluated by calculating the following, widely accepted, parameters: mean of RR and its standard deviation (STD RR) also called SDNN in ms, square root of the mean squared differences of successive RRi (rMSSD) in ms, and geometrical forms as the integral of the RRi histogram divided by the height of the histogram (RR tri index) and the baseline width of the RRi histogram (TINN) in ms (1).

To summarize, STD RR represents a global index of HRV (overall HRV) and reflects all the cyclic components responsible for variability in the recording period, rMSSD reflect alterations in autonomic tone that are predominantly vagally mediated and the geometrical HRV indexes are an estimate of the overall HRV (22). This multivariate approach allows for a comprehensive assessment of CA function.

Data statistical analysis

Sample size calculation, based on a previous study (23), suggested that recruitment of 12 patients in each group would provide sufficient statistical power (80.0%) to detect a clinically important difference in the ApEn. Differences between the two groups (pre-operative and first post-operative data) were assessed by the unpaired Student's *t*-test for continuous variables and by the Fisher's exact test for categorical variables. The effect of time (first post-operative day (T1) compared with discharge day (T2), i.e. effect of CR); group (LVF normal compared with LVF reduced) and the interaction between time and group effects were evaluated by two-way analysis of variance (ANOVA) for repeated measures. When an interaction was found, the simple main effects were analysed (difference between changes (post-CR – pre-CR) for each group by unpaired Student's *t*-test) and Cohen's *d* effect sizes were calculated for these mean differences. Data are reported as mean ± SD, unless otherwise specified. A p-value < 0.05 was used to define statistical significance for all tests. Statistical analyses were carried out with software Statistica 5.5 (StatSoft Inc., Tulsa, USA) and SPSS 10.0 (Chicago, IL, USA).

RESULTS

Flow of participants through the trial and characteristics

A total of 108 patients were evaluated over a 2-year period for possible enrollment. Twenty-three patients were excluded secondary to not meeting the inclusion criteria and 2 declined to participate. The remaining 83 patients enrolled, and from this cohort, 6 patients died, 8 did not undergo surgery, 13 underwent surgery without cardiopulmonary bypass, 3 discontinued the intervention, 2 presented with medical complications and 7 had poor-quality HR signals. Finally, 23 patients were assigned to the LVFN and 21 patients to the LVFR group for analyses. The flow of participants through the trial is shown in Fig. 1.

The basic clinical, operative and HRV data during the pre-operative (T0) assessment for the studied cohort are summarized in Table II. With the exception of LVEF, no differences were observed between groups initially with respect to clinical or demographic data, including age, height, gender and BMI. Six patients in the LVFN group and 5 in the LVFR group presented with a BMI > 30 kg/m^2, but none of the subjects were > 35 kg/m^2. Furthermore, the cardiovascular risk factor profile was similar between the two groups (i.e. smoking, arterial hypertension, diabetes mellitus and dyslipidemia history). Lastly, the groups had similar pharmacological treatment profiles.

The surgical procedure data were comparable between groups, demonstrated by similar cardiopulmonary bypass time, aortic cross-clamping time, total surgery time and number of graft anastomoses. In addition, the time of hospital stay after surgery was similar between groups.

With respect to baseline HRV (T0), patients in the LVFN group presented with significantly greater values of time domain measures (rMSSD, STD RR, RR tri index, TINN) as well as SD1, a non-linear HRV index ($p < 0.05$) compared with the LVFR group.

Compliance with trial methodology

All patients included in the analysis (44 patients) participated in a once-daily supervised post-operative exercise protocol, starting at the first post-operative day until discharge (approximately 5 days). However, 3 patients refused to continue the protocol, primarily because participants reported unwillingness to undertake physical exercise at that moment. Thus patients who did not undergo one phase of CR were excluded from final analysis.

No clinically relevant adverse events occurred throughout the study. Vital signs (blood pressure, respiratory rate and body temperature) remained within the range of normality in both preserved and depressed LVF patients. According to the VRS-4 scale, pain was present post-operatively, but did not differ between the first post-operative day and discharge either within or between groups (first post-operative day VRS-4 = 2 (SD 0.4) and 1.9 (SD 0.7) and discharge VRS-4 = 1.6 (SD 0.5) and 1.6 (SD 0.7) to LVFN vs LVFR, respectively).

As demonstrated in Table II, the pharmacological treatment profile was also similar between groups throughout the study.

Heart rate variability

On the first post-operative day, i.e. after the surgery and before CR, the non-linear and linear HRV indexes did not differ significantly ($p > 0.05$) between LVFN and LVFR groups (data not shown). Both groups participated in the inpatient CR

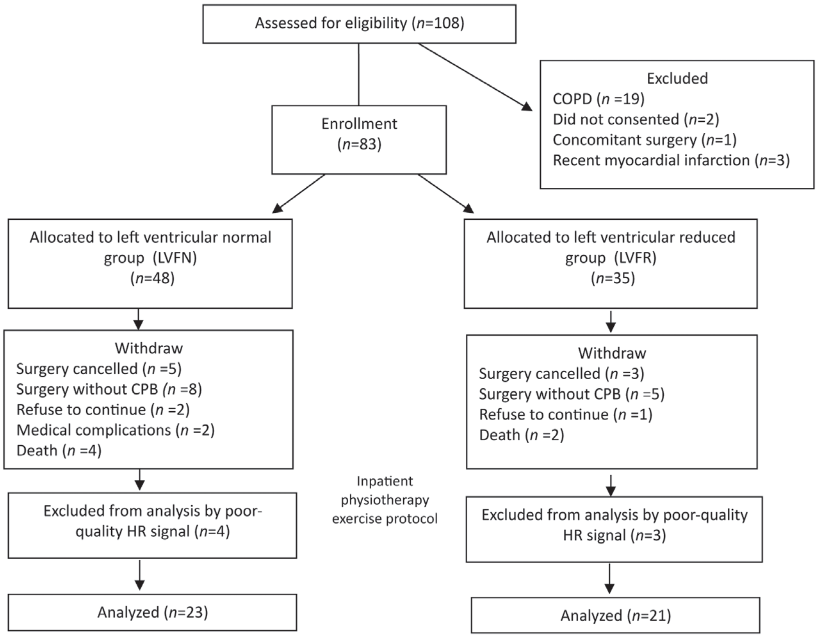

Fig. 1. Patient's participation.

Table II. *Basic clinical, operative and pre-operative heart rate variability data*

	LVFN group, *n*=23	LVFR group, *n*=21	*p*-value
Age, years, mean (SD)	60 (9.5)	56 (7.8)	0.22
Male, *n* %	17 (73.9)	16 (76.2)	1.00
Weight, kg, mean (SD)	75 (13)	73 (14)	0.59
Height, m, mean (SD)	1.6 (0.08)	1.6 (0.06)	0.91
Body mass index, kg/m^2, mean (SD)	27 (4.0)	27 (5.0)	0.66
Left ventricular ejection fraction, %	61.7 (5.7)	43.8 (4.7)	0.0001
Risk factors, *n* %			
Smoking history	17 (73.9)	19 (90.5)	0.45
Arterial hypertension	18 (78.3)	15 (71.4)	0.73
Diabetes mellitus	7 (30.4)	11 (52.4)	0.22
Dyslipidemia	11 (47.8)	12 (57.1)	0.56
Pharmacological treatment, *n* (%)			
β-blockers	15 (65.2)	15 (71.4)	0.75
ACE inhibitors	10 (43.5)	8 (38.1)	0.76
Calcium antagonists	1 (4.3)	–	1.00
Per- and post-operative data			
CPB time, min, mean (SD)	68 (21)	69 (22)	0.70
ACCT, min, mean (SD)	37 (14)	36 (12)	0.79
Operation duration, min, mean (SD)	182 (60)	215 (69)	0.11
Distal anastomoses, *n* (%)	2.6 (0.6)	2.5 (0.6)	0.82
Post-operative hospital stay, days, mean (SD)	5.1 (1.1)	4.6 (0.9)	0.23
Non-linear heart rate variability, mean (SD)			
Approximate entropy	1.1 (0.07)	1.0 (0.08)	0.08
Correlation dimension	0.81 (1.0)	0.40 (0.46)	0.06
SD1, ms	15 (5.6)	9.9 (5.2)	0.008
SD2, ms	37 (19)	29 (15)	0.17
Linear heart rate variability, mean (SD)			
Mean RR, ms	963 (134)	911 (157)	0.26
STD RR, ms	20 (5.5)	15 (7.5)	0.01
rMSSD, ms	20 (8.2)	15 (8.2)	0.04
RR tri index	5.7 (1.8)	4.4 (1.9)	0.03
TINN, ms	92 (29)	68 (34)	0.02

LVFN: left ventricular function normal; LVFR: left ventricular function reduced; ACE: angiotensin converting enzyme; CPB: cardiopulmonary bypass; ACCT: aortic cross-clamping time; HRV: heart rate variability; SD: standard deviation; STD RR: standard deviation of RR; rMSSD: square root of the mean squared differences of successive RR; RR tri: integral of the RR histogram divided by the height of the histogram; RR: RR intervals (intervals between two consecutive cardiac beats); TINN: baseline width of the RR histogram.

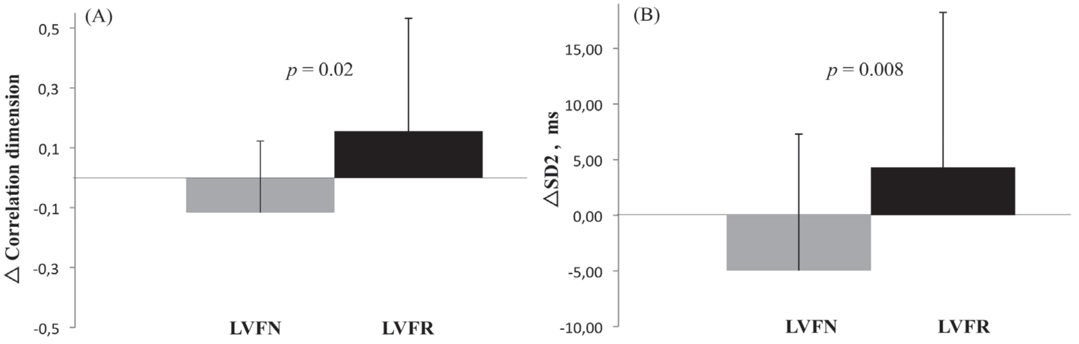

Fig. 2. Changes in heart rate variability parameters between left ventricular function normal (LVFN) and reduced (LVFR) group. (A) Correlation dimension. (B): SD2. LVFN (grey bars); LVFR (black bars). Changes were calculated as (post-rehabilitation (discharge) – pre-rehabilitation (first post-operative)). Error bars refer to standard deviation.

exercise-based program for the same duration (5.1 days (SD 1.1) for LFVN vs 4.6 days (SD 0.9) for LFVR).

A two-way ANOVA was conducted to examine the effect of time (effect of CR) and group (LVFN vs LVFR) on HRV data (Table III). There were statistical differences in non-linear HRV indexes, CD and SD2 according to time and group ((e.g. interaction time (effect of CR) vs group (LVFN vs LVFR)), $p = 0.04$. Thus, these results describe the simultaneous influence of ventricular function and CR held the first day after surgery until discharge on non-linear HRV indexes. There was also a significant time effect on mean RR ($p = 0.03$) and rMSSD ($p = 0.02$) indexes.

A simple main effects analysis showed that the LFVR patients had significantly greater improvements in CD and SD2 ($p < 0.05$) compared with LFVN patients after attending a short-term supervised inpatient CR program, which is illustrated in Fig. 2. In addition, the mean effect size (Cohen's *d*) was $d = 0.71$ (95% confidence interval (CI) = –17.6 to –0.86) for SD2 and $d = 0.92$ (95% CI = –0.47 to –0.07), for CD, a significant medium to large effect, respectively.

DISCUSSION

Summary of findings

The main finding of the study is that post-CABG patients undergoing an inpatient CR exercise-based program with reduced LVF demonstrated greater beneficial CA adaptation, as shown by greater non-linear HRV parameters (SD2 and CD) on discharge, when contrasted with patients with normal LVF undergoing the same CR intervention.

Importance of this study

This is the first study, to our knowledge, to assess the CA adaptations in patients with varying LVF profiles undergoing CABG and an inpatient CR exercise-based program. Previous

Table III. *Non-linear and linear heart rate variability data, during resting supine condition for both groups*

	LVFN group		LVFR group		*p*-value		
	T1 Mean (SD)	T2 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	Time	Group	Interaction
Non-linear HRV							
Approximate entropy	1.1 (0.2)	1.1 (0.1)	1.0 (0.1)	1.1 (0.1)	0.09	0.37	0.14
Correlation dimension	0.2 (0.3)	0.04 (0.1)	0.1 (0.1)	0.2 (0.3)	0.57	0.51	0.04**
SD1, ms	5.9 (3.6)	7.4 (4.0)	7.4 (5.6)	9.5 (6.3)	0.14	0.21	0.85
SD2, ms	20.6 (14.0)	14.4 (5.0)	15.9 (6.2)	19.8 (12.3)	0.82	0.75	0.04**
Linear HRV							
Mean RR, ms	716.3 (87.5)	753.9 (75.1)	689.1 (103.4)	739.8 (110.6)	0.02*	0.47	0.53
STD RR, ms	9.7 (6.1)	7.7 (2.7)	9.4 (4.9)	11.6 (6.2)	0.96	0.16	0.27
rMSSD, ms	8.3 (5.1)	9.7 (5.7)	9.4 (6.7)	12.8 (8.8)	0.03*	0.24	0.64
RR tri index	2.9 (1.3)	2.6 (0.9)	2.9 (1.2)	3.5 (1.7)	0.75	0.08	0.08
TINN, ms	46.2 (22.8)	38.4 (14.7)	43.1 (21.1)	50.8 (25.9)	0.81	0.25	0.19

LVFN: left ventricular function normal; LVFR: left ventricular function reduced; T1: pre-cardiac rehabilitation (first post-operative day); T2: post-cardiac rehabilitation (discharge day); HRV: heart rate variability; SD: standard deviation; RR: RR intervals; STD RR: standard deviation of RR; rMSSD: square root of the mean squared differences of successive RR; RR tri: integral of the RR histogram divided by the height of the histogram; TINN: baseline width of the RR histogram. Analysis of variance2-way: *significant time effect (T1 vs T2); **significant interaction between group and time effects.

investigators (11, 24) have reported that benefits from exercise training and CR appeared greatest in patients with LV dysfunction; however, the majority of these studies involved outpatient CR as the intervention.

Although one study (11) has evaluated the effects of physical training in patients with poor LVF soon after cardiac surgery, the main outcome involved was the 6-min walk test distance and not changes in CA characteristics. Thus, a novel aspect of this study was that there is a simultaneous influence of ventricular function and CR (first day after surgery until discharge) on CA adaptation, verified by the significant interaction between time and group.

Therefore, inpatient exercise-based CR should be particularly considered for post-CABG patients with poor LVF to promote beneficial CA adaptations, among other things. This is an important consideration, since electrical instability may occur after CABG, increasing the risk for adverse events.

Effect of intervention between left ventricular funcion normal and left ventricular ejection fraction groups

There is strong evidence to support the use of exercise-based CR in patients with reduced LVF, as well as those with normal LVF who have undergone bypass surgery (25).

Our group (10), as well as others (26), reported a significant improvement in CA function at hospital discharge following a progressive inpatient exercise protocol in patients post-CABG and post-acute myocardial infarction, respectively. Thus, these studies were able to demonstrate that, even in a short period, exercise-based CR might be an effective tool for improving CA tone.

However, if patients with reduced LVF could attain a greater benefit from this type of rehabilitation program required further investigation. In this context, the present study was conducted considering the inherent differences in LVF. We demonstrated a more beneficial CA adaptation in patients with reduced LVF, evidenced by greater improvements in HRV parameters after CR compared with patients with normal LVF who received the same treatment.

Since the design and focus of the present study is unprecedented we had difficulties in directly comparing our findings against any existing studies. Notwithstanding, several reports also confirm that exercise training can modulate cardiovascular autonomic tone, shifting it toward a lower sympathetic tone and a higher vagal tone in healthy subjects and patients with cardiovascular disorders (7, 27, 28). However, most studies conducted long-term CR on outpatients without controlling for LVF.

Cardiac neural regulation was analysed by association between traditional time domain measures, as well as non-linear measures of HRV. In this study, we found non-linear indexes (SD2 and CD) were influenced by the time and group interaction ((e.g. interaction time (effect of CR) vs group (LVFN vs LVFR)); with significantly higher SD2 and CD values being obtained in patients undertaking inpatient CR with reduced LVF.

In addition, the mean effect sizes (Cohen's d) found were $d=0.71$ and 0.92 for SD2 and CD, respectively, which is characterized as a significant medium to large effect. According to Wolf (29) a Cohen's $d>0.50$ is clinically significant, indicating the findings of the current study are of substantial clinical impact.

The SD2 measure has been shown to be related to the linear SDNN (STDRR) index, a global measure of HRV (1). In this context, other authors demonstrated that improvements in global measures, such as SDNN, have been linked to a reduction in cardiovascular risk (30).

Another consideration of the non-linear HRV findings in the current study was the higher values of CD in patients with reduced LVF. A decrease in CD has been found during stressful conditions (20), hypertension and obstructive sleep apnea (31), and marks an impairment of autonomic nervous system control of heart rate.

Therefore, non-linear HRV indexes have been used to estimate the complexity of heart rate dynamics, since the heart rate exhibits chaotic properties and in general, reduced complexity in heart rate dynamics may represent a lower adaptability of the cardiac pacemaker and functional restriction of the participating cardiovascular elements (20).

In the context of cardiac surgery, the reduced complexity in heart rate has been shown to be associated with post-operative complications after vascular surgery, such as myocardial infarction, unstable angina, congestive heart failure and prolonged inotropic support (32, 33). Thus, the findings of the current study indicate subjects with reduced LVF, who are perhaps at great risk for autonomic-related events, may benefit substantially from the early initiation of an inpatient CR program.

In addition, the linear indexes, mean RR and rMSSD demonstrated a significant time effect, suggesting that these indices changed during hospitalization in patients undergoing CABG and CR. However, no time vs group interaction was found. rMSSD is a time-domain index of HRV and has parasympathetic modulation as the major mechanism (1, 28), thus representing beneficial adaptations in these linear measures for both groups independently.

In this study, as also observed in a previous investigation (31), non-linear measures of HRV appear to be more sensitive in detecting the difference in the autonomic adaptations between patients with normal and reduced LVF undergoing CABG after rehabilitation compared with linear measures.

In this context, although the patients with reduced LVF showed better results, it is important to note that previous studies (28, 34) observed acute HRV impairment post-CABG, irrespective of LVF. This impairment has been related to long-term bed-rest (23). Therefore, early mobilization and exercise training on an inpatient basis may be broadly warranted after CABG, both in patients with reduced LVF as those with preserved cardiac function.

Interestingly, one study (35) has shown that respiratory training could have a conditioning effect on cardiac vagal tone. The beneficial influence was postulated to be due to ventilation levels reached during this type of training being similar to those achieved in mild whole body exercise. In our study, the improvement of vagal control on heart rate in the reduced LVF group could also have been affected by respiratory exercises. However, it was not possible to quantify and distinguish this influence from the other components of the training program and further research is required.

Impaired cardiac function is associated with enhanced activity of the sympathetic nervous system and parasympathetic nervous system suppression is an attempt to preserve cardiac function (23). In addition, studies have demonstrated that patients with poorer clinical status at baseline are likely to derive more benefit from interventions (8, 11, 36). For example, Tygesen et al. (8), showed a greater improvement in HRV after exercise training in post-CABG patients compared with a post-myocardial infarction cohort. The authors attributed this finding to lower basal HRV in the former group and thus the greatest potential for improvement.

Another important aspect in this study was the prevalence of a clinical diagnosis of diabetes in both groups (30.4% in LVFR vs 54.4% in LVFN group, with a difference of 22% between groups, $p > 0.05$), although no patient presented diabetic neuropathy. Diabetes is common in patients undergoing CABG and leads to impaired HRV (37). However, in an analysis of these subgroups, we observed that this finding did not influence our results.

In our study, although the reduced LVF group presented with lower HRV at baseline, the beneficial adaptation was superior in several HRV indexes, a finding consistent with previous investigations. Moreover, some HRV indexes (CD, SD2) worsened (mean values) in the LVFN group, and improved in the LVFR group, which may have reinforced the differences found between the groups.

Limitations

The generalization of our findings may be restricted secondary to the characteristics of patient recruitment. Specifically, patients with severely reduced LVF (LVEF < 30%) were not included in the current study because they represented a minority of the cases for CABG in the hospital where the study was conducted. Therefore, we cannot determine if the same beneficial effects on inpatient exercise training on HRV occur in patients with particularly poor LVF.

Another important limitation of this study was the absence of a control group (without physical treatment). However, in a previous randomized controlled trial (10), we demonstrated the efficacy of a short-term supervised inpatient physiotherapy exercise program in improving HRV indexes in CABG patients. While, our previous findings support the beneficial impact of inpatient CR on HRV in the present study, future research in this area should be conducted utilizing a randomized controlled design.

Clinical implications

Autonomic imbalance is known to adversely affect clinical outcome in patients with cardiac disease. The results of the current study support the use of early CR in order to, among other things, improve CA function. While outpatient CR is well established, less focus is given to the importance of the inpatient phase of rehabilitation. Our findings warrant a stronger consideration for the implementation of structured exercise programs in the inpatient setting.

In the framework of cardiac autonomic function, the findings of our research provide evidence that after CABG, patients with depressed LVF are precisely those who experienced significantly more marked benefits at the end of short-term inpatient rehabilitation without taking additional risks. Notwithstanding, our study does not elucidate the mechanism by which the different adaptations occur after rehabilitation.

In conclusion, our data show that, among patients undergoing CABG and engaged in a short-term inpatient rehabilitation program, those with reduced LVF are most likely to have better cardiac autonomic adaptations to exercise-based rehabilitation without encountering additional risks.

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