[Original article]

Modulating effect of cardiac rehabilitation on autonomic nervous system function in patients with coronary artery disease

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Introduction   Autonomic nervous system (ANS) dysfunction is associated with prognosis in coronary artery disease (CAD). We aimed to study the cardiac rehabilitation (CR) modulating effect on autonomic function, through heart rate variability (HRV) and heart rate recovery (HRR) after exercise, in CAD patients and the associated factors.

Methods   This study is a retrospective analysis of CAD patients in sinus rhythm who complete a single-centre CR programme and complementary evaluation including HRV study, cardiopulmonary exercise testing, echocardiogram.

Results   Our sample included 142 CAD patients (85.9% male, 57.8 ± 10.2 years, 85% post-acute coronary syndrome, 15% stable CAD). There was a significant improvement in SDNN (120.7 ± 40.7 ms vs 127.6 ± 41.5 ms; P = 0.019), resting HR (71.3 ± 10.7 min^{-1} vs 69.0 ± 10.9 min^{-1}; P = 0.015) and HRR (23.8 ± 12.3 min^{-1} vs 27.1 ± 12.5 min^{-1}; P = 0.017) following CR. Lower erythrocyte sedimentation rate (OR 0.911; 95% confidence interval (CI) 0.838-0.989, P = 0.027), normal left ventricular (LV) function/mild LV systolic dysfunction (OR 7.879; 95% CI 2.753-17.351, P = 0.009) and SDNN lower than 100 ms (OR 9.325; 95% CI 1.775-48.978, P = 0.008) were independently associated with SDNN improvement; quit smoking (OR 4.323; 95% CI 1.136-16.454, P = 0.014) and abnormal HRR (OR 8.023; 95% CI 1.049-64.811, P = 0.035) were independently associated with HRR improvement.

Conclusion   The cardiac rehabilitation programme induced a positive modulation of the autonomic function in CAD patients, as reflected by SDNN and HRR improvement. This benefit was associated with ANS baseline dysfunction, lower systemic inflammation, quit smoking and normal LV function to mild left ventricular systolic dysfunction.

Keywords   *Autonomic nervous system – cardiac rehabilitation – coronary artery disease; heart rate recovery – heart rate variability.*

INTRODUCTION

Autonomic nervous system (ANS) dysfunction is associated with increased risk of morbidity and mortality in coronary artery disease (CAD), especially the risk of

sudden cardiac death[1,2]. Previous data have shown an increase of sympathetic nervous activity and decrease of vagal tone after an acute coronary syndrome[3,4]. Autonomic function may be assessed by relatively easy, non-invasive and cost-effective methods as resting heart rate (HR), heart rate variability (HRV), which analyse variation in the intervals between consecutive normal heart beats in milliseconds, and heart rate recovery (HRR) in exercise testing, that can be defined as the reduction in the heart rate from the rate at peak exercise to the rate one minute after the cessation of exercise[5,6]. Exercise-based cardiac rehabilitation (CR) has been associated with positive effects on autonomic function in CAD patients[7,8], with HRV and HRR increases. This improvement in autonomic balance seems to correlate with increased

exercise capacity, although few studies identified the parameters associated with ANS function modification.

We aimed to evaluate the modulating effect of CR on ANS function in CAD patients and to identify CAD risk factors and functional parameters associated with ANS function modification.

METHODS

CAD patients who completed a phase-2 CR programme and pre- and post-CR complementary evaluation in our centre between January 2004 and January 2013 were retrospectively evaluated. Patients with a pacemaker or atrial fibrillation and those who failed to attend at least 80% of the exercise sessions or did not complete all the complementary evaluation were excluded.

In ACS patients, pre-CR evaluation was performed in the first 2 weeks and the phase-2 CR programme was initiated between 2-4 weeks after discharge.

CR programme

The CR programme consisted of 12 weeks of exercise training and lifestyle modification. The exercise training programme was performed three days per week (36 sessions). Each exercise session included 10 minutes of warm-up, 30 minutes of aerobic exercise, 10 minutes of muscular strengthening and 5 minutes of cooling down and stretching. In the exercise prescription, the maximal exercise intensity was calculated as a percentage of the heart rate achieved at the anaerobic threshold in the treadmill exercise test. Individualized exercise prescription was periodically adjusted to encourage a gradual increase in overall exercise performance.

In addition to the supervised exercise sessions, each patient was encouraged to exercise daily outside the formal exercise programme. All patients received dietary counselling by a nutrition specialist and selected patients received psychological support with self-management behaviour and underwent smoking cessation consult.

Complementary evaluation

The complementary evaluation consisted of an immediate pre- and post-CR HRV study, cardiopulmonary exercise testing (CPT) and transthoracic echocardiography.

The HRV study was based on a 24-hour Holter recording by analysing the standard deviation of the NN (regular R-R) intervals (SDNN).

Before treadmill exercise testing, the resting haemodynamic parameters (HR, systolic and diastolic blood pressure) were measured. Resting HR was measured fifteen minutes before the onset of the stress test and after the patient had remained in a supine position for at least five minutes, in a quiet, mild-temperature environment. With the patient seated, basal blood pressure was obtained by the mean of two measurements with a 1-min interval, using a digital automatic blood pressure monitor. For systolic blood pressure, if there was more than 5 mmHg difference between the two readings, a third reading was obtained for the mean determination. Pharmacologic therapy, namely beta blockers, was maintained during pre- and post-CR evaluation. Non-smoking was strictly recommended on the day of the test. Then, a symptom-limited treadmill exercise test was conducted according to the modified Bruce protocol. The HR was monitored during the test and averaged every 10 seconds, using 12-lead electrocardiogram readings. Peak HR was considered the highest value achieved during the test. Blood pressure was measured with a mercury sphygmomanometer during the last 45 seconds of each stage of exercise, and in the last 15 seconds of exercise, nearing the end of the test. Peak systolic and diastolic blood pressures were recorded as the highest value achieved during the test. HRR was determined by calculating the difference between HR at peak exercise and HR at one minute after completion of the exercise. HR reserve was defined as the difference between peak and resting HR. Patients were instructed to sit after ending the test, and there was no cool-down. Pulmonary gas exchange analysis was performed throughout the test, including the measurement of oxygen uptake (VO_2) (SensorMedics Vmax 229, Yorba Linda, Calif.). Peak VO_2 (pVO_2) was defined as the highest VO_2 attained during the final 30 seconds of exercise. By transthoracic echocardiography, the left ventricular ejection fraction (LVEF) (Simpson's biplane method) and the E/A ratio were determined.

Statistical analysis

Discrete data are expressed as frequency (percentage) and continuous variables as mean ± SD, or as median (minimum–maximum), when appropriate. Pre- and post-CR data were compared using the Student's independent t-test. The association of clinical and demographic characteristics, natriuretic peptides levels, CPT and echocardiographic parameters with SDNN and HRR improvement were studied using the chi-square test or the Student's independent t-test and by backward multivariate logistic regression analysis, using significant variables. Data were analysed using the SPSS version 17.0 statistical software and the level of statistical significance was $\alpha = 0.05$.

RESULTS

Our sample included 142 patients (85.9% male, 57.8 ± 10.2 years), 85% post-acute coronary syndromes of which 91 patients (64%) were in the first month following ST-segment elevation myocardial infarction (76% had percutaneous coronary intervention complete revascularization), and 15% had stable CAD. The clinical characteristics of the sample are presented in table 1. All patients were on antiplatelet therapy, statin, and a stable dose of beta blockers.

Pre- and post-CR data are presented in table 2. There were significant improvements in SDNN (Δ 6.9 ± 34.5 ms; 120.7 ± 40.7 vs 127.6 ± 41.5 ms, $P = 0.019$), resting HR (Δ 2.4 ± 11.0 min^{-1}; 71.3 ± 10.7 vs 69.0 ± 10.9 min^{-1}, $P = 0.015$), peak HR (Δ 2.8 ± 14.7 min^{-1}; 138.3 ± 21.0 vs 141.2 ± 21.3 min^{-1}, $P = 0.027$), HR reserve (Δ 3.3 ± 15.6 min^{-1}; 67.0 ± 20.1 vs 72.2 ± 20.0 min^{-1}, $P < 0.001$), HRR (Δ 3.3 ± 15.6 min^{-1}; 23.8 ± 12.3 vs 27.1 ± 12.5 min^{-1}, $P = 0.017$), pVO$_2$ (Δ 1.8 ± 6.0 mL.kg. min^{-1}; 25.6 ± 6.8 vs 27.5 ± 7.2 mL.kg. min^{-1}, $P = 0.001$) and E/A ratio (Δ −0.15 ± 0.45; 1.20 ± 0.54 vs 1.06 ± 0.39, $P < 0.001$).

The baseline independent factors associated with SDNN improvement were ESR (OR 0.911; 95% confidence intervals (CI) 0.838-0.989, $P = 0.027$), LVEF > 40% (OR 7.879; 95% CI 2.753-37.351, $P = 0.009$) and SDNN < 100 ms (OR 9.325; 95% CI 1.775-48.978, $P = 0.008$) as presented in table 3. The independent predictors of HRR improvement were baseline abnormal HRR (OR 8.023; 95% CI 1.049-64.811, $P = 0.035$) and quit smoking (OR 4.323; 95% CI 1.136-16.454, $P = 0.014$).

DISCUSSION

In this retrospective cohort we evaluated the modulating effect of CR on ANS function in CAD patients and identified the clinical and functional parameters associated with ANS function modification.

Autonomic function was assessed using three different techniques: resting HR, HRV and HRR, which have been previously validated[5,6].

These parameters reflect the balance of sympathetic and parasympathetic effects, and their interactions. Each of these compounds had prognostic significance in primary and secondary prevention settings, even though a pathophysiological link has not been established. In the general population, the decrease of HRV and high resting HR can mean an increased risk of coronary heart disease, death and cardiac mortality[7-9], whereas abnormal HRR increases the relative risk of death[10].

In patients with cardiovascular disease, ANS dysfunction is associated with worse prognosis[2]and might be a therapeutic target. Decreased HRV has been associated with increased mortality and sudden death[11]. Likewise, HR correlates with mortality and cardiac events[12]. Also in this group, decreased HRR is an independent predictor of mortality[13].

Table 1 Clinical characteristics of the sample

	Total n = 142
Age, mean (SD), (years)	57.8 (10.2)
Male, n (%)	122 (85.9)
Sedentary (no regular physical exercise), n (%)	98 (69)
Smoking, n (%)	60 (42)
Dyslipidaemia, n (%)	86 (61)
Arterial hypertension, n (%)	71 (50)
BMI, mean (SD) (Kg/m²)	27.7 ± 3.8
Obesity, n (%)	38 (27)
Diabetes mellitus, n (%)	23 (16)
Family history of cardiovascular disease, n (%)	21 (15)
Prior MI, n (%)	19 (13)
SBP, mean (SD) (mmHg)	121 ± 15
DBP, mean (SD) (mmHg)	72 ± 10
STEMI, n (%)	91 (64)
NSTEMI, n (%)	30 (21)
Stable CAD, n (%)	21 (15)
Multivessel disease, n (%)	58 (41)
NYHA function class ≥ 2, n (%)	42 (30)
Creatinine (mg/dL , mean (SD)	0.93 ± 0.23
eGFR (mL/min per 1.72 m²), mean (SD)	101 ± 34
hs-CRP (mg/dL), mean (SD)	13.4 ± 24.9
Erythrocyte sedimentation rate (mm/h), mean (SD)	13.5 ± 17.9
Fasting glycaemia, mean (SD) (mg/dL)	110 ± 26
Total cholesterol, mean (SD) (mg/dL)	153 ± 35
LDL-cholesterol, mean (SD) (mg/dL)	96 ± 29
HDL-cholesterol, mean (SD) (mg/dL)	39 ± 11
Triglycerides, mean (SD) (mg/dL)	109 ± 57
LVEF, mean (SD) (%)	54.3 ± 10.3
LVEDD, mean (SD) (mm)	54.4 ± 8.5
LVESD, mean (SD) (mm)	35.7 ± 9.6
IVST, mean (SD) (mm)	10.3 ± 2.3
PWT, mean (SD) (mm)	9.5 ± 1.8
LV mass, mean (SD) (g/m²)	99.8 ± 35

Values are mean ± SD or N (%). BMI: body mass index, MI: myocardial infarction, SBP: systolic blood pressure, DBP: diastolic blood pressure, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, CAD, coronary artery disease, NYHA: New York Heart Association, eGFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, LDL: low-density lipoprotein, HDL: high-density lipoprotein, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVST: interventricular septal thickness, PWT: posterior wall thickness, LV mass: left ventricular mass.

Table 2 Pre- and post-cardiac rehabilitation data

	Pre-CR	Post-CR	P-value
Standard deviation of the NN intervals (ms)	120.7 ± 40.7	127.6 ± 41.5	0.019
Resting heart rate (min⁻¹)	71.3 ± 10.7	69.0 ± 10.9	0.015
Peak heart rate (min⁻¹)	138.3 ± 21.0	141.2 ± 21.3	0.027
Basal systolic blood pressure (mmHg)	121.3 ± 15.0	119.6 ± 14.8	0.311
Basal diastolic blood pressure (mmHg)	71.5 ± 9.9	71.6 ± 10.7	0.866
Peak systolic blood pressure (mmHg)	171.6 ± 24.9	170.6 ± 22.6	0.654
Peak diastolic blood pressure (mmHg)	82.3 ± 11.6	80.5 ± 10.2	0.160
Heart rate reserve (min⁻¹)	67.0 ± 20.1	72.2 ± 20.0	< 0.001
Heart rate recovery (min⁻¹)	23.8 ± 12.3	27.1 ± 12.5	0.017
Cardiopulmonary testing duration (min)	13.5 ± 3.2	15.3 ± 2.4	0.140
Peak oxygen consumption (mL.kg.min⁻¹)	25.6 ± 6.8	27.5 ± 7.2	0.001
Left ventricular ejection fraction (%)	54.3 ± 10.3	54.9 ± 10.4	0.192
E/A ratio	1.20 ± 0.54	1.06 ± 0.39	< 0.001

Values are mean ± SD.

Table 3 Factors associated with SDNN and HRR improvement

Variable	Univariable analysis Odds ratio (95% CI)	P-value	Multivariable analysis Odds ratio (95% CI)	P-value
SDNN improvement				
Obesity	2.444 (1.077-5.544)	0.033	1.623 (0.402-6.543)	0.496
ESR	0.964 (0.929-1.000)	0.047	0.911 (0.838-0.989)	0.027
LVEF > 40%	3.292 (1.061-10.209)	0.039	7.879 (2.753-17.351)	0.009
E/A ratio	2.667 (1.140-6.243)	0.024	3.388 (0.678-16.916)	0.137
SDNN < 100 ms	4.577 (2.047-10.232)	< 0.001	9.325 (1.775-48.978)	0.008
HRR improvement				
Quit smoking	3.857 (1.236-12.040)	0.020	4.323 (1.136-16.454)	0.014
Abnormal HRR	18.655 (2.412-144.276)	0.005	8.023 (1.049-64.811)	0.035
LVEF < 35%	0.092 (0.011-0.772)	0.028	0.115 (0.008-1.642)	0.111

SDNN: standard deviation of the NN (regular R-R) intervals, ESR: erythrocyte sedimentation rate, LVEF: left ventricular ejection fraction, HHR: heart rate recovery.

Another advantage of the autonomic nervous system evaluation through these three parameters is that they are easy to use and inexpensive. It may be a powerful and convenient tool for risk stratification and for monitoring the improvement after exercise training in patients with coronary artery disease.

We must point out that rest HR and HR response was influenced by therapy, however, patients have been evaluated pre- and post-CR with the same therapy, including beta blockers.

The CR programme was associated with a significant improvement in ANS function as assessed by the three parameters. In this study we observed a significant improvement of the resting HR (Δ 2.4±11.0 min⁻¹; 71.3±10.7 vs 69.0±10.9 min⁻¹, P=0.015) and HRR (Δ 3.3±15.6 min⁻¹; 23.8±12.3 vs 27.1±12.5 min⁻¹,

P=0.017). Other studies previously demonstrated similar benefits after exercise training[14,15]. Ribeiro et al.[15] in a well-designed prospective, randomized, controlled trial, found an improvement of resting HR by 5.5 min⁻¹ and an increase of HRR by 4 min⁻¹, in the training group, after 8 weeks of aerobic exercise, whereas the control group remained unchanged.

After exercise, the interval of HRR predominantly results from parasympathetic reactivation with sympathetic and non-autonomic components playing minor roles. Exercise-based cardiac rehabilitation has been shown to reduce total mortality, cardiac mortality, hospital admissions[16] and sudden death[17]. Therefore, one acceptable reason for the improvement of these outcomes is the autonomic function modification, mainly reflecting the antiarrhythmic characteristic of the

parasympathetic nervous system[18]. Other improvements of ANS, after exercise training, sharing similar pathophysiological mechanisms, are the increased resting arterial baroreflex sensitivity, the decrease in muscle sympathetic nerve activity, and the reduced circulating catecholamines and angiotensin II levels[19].

It is difficult to know if there is a clinical advantage in continuously improving the HRR or resting HR. Jouven et al.[9] reported, in a cohort of asymptomatic working men, that a HRR < 25 bpm after the first minute of recovery provides a relative risk of 2.2 of sudden cardiac death compared with the highest-percentile HRR group (> 40 bpm). A RHR > 75 bpm conferred a relative risk for sudden death of 3.9 compared with the lowest-percentile resting HR group (< 60 bpm). There seems to be a continuous relationship between prognostic and resting HR, with no observed threshold[10]. In this study, patients with decreased HRR achieved greater improvements in this parameter (< 12 bpm, n = 20 – Δ 19.1 ± 14.1 ms; < 25 bpm, n = 72 – Δ 9.8 ± 14.8 ms, $P < 0.001$).

Another non-invasive parameter of ANS is HRV, which is the oscillation in the intervals between consecutive heartbeats. Commonly used time domain measures of HRV include standard deviation of normal R-R intervals (SDNN) which are also thought to be a marker of parasympathetic cardiac modulation. It is accepted that some therapies may improve outcomes by an increase of HRV. This is true for patients with heart failure who are subject to cardiac resynchronization therapy[20] and to exercise training[21]. Significant improvements in HRV in myocardial infarction patients with exercise were reported in some controlled trials[22].

In the present study there was a significant improvement of the SDNN after CR (Δ 6.9 ± 34.5 ms; 120.7 ± 40.7 ms vs 127.6 ± 41.5 ms, $P = 0.019$), and patients with lower SDNN (< 100 ms, n = 51) had greater improvement (Δ 31.2 ± 50.0% vs −0.6 ± 20.7%, $P < 0.001$). It is difficult to define a cut-off value of SDNN that defines impaired HRV and a threshold for no more improvement in outcomes. In this cohort high baseline HRV values correlate with less increase in SDNN and plateau has been previously described[23].

Few studies have previously identified the characteristics associated with ANS function modification. In our cohort, lower erythrocyte sedimentation rate, normal or mild systolic dysfunction and tobacco cessation were independent predictors of improved ANS.

In the literature an association is described between inflammation and autonomic dysfunction in CAD patients[24,25] and this combination seems to have a synergistic effect[26]. The "inflammatory reflex" proposed by Tracey[27] suggests that the activation of the vagal nerve leads to reduced production of inflammatory cytokines, thus the increase in vagal activation induced by exercise

training could be an important mechanism to improve the inflammatory status[28]. Whelton et al.[29] found that an elevated resting heart rate is independently associated with elevated inflammatory biomarkers, such as high-sensitivity C-reactive protein, even after adjustment for physical activity levels. Our results, of better improvement of SDNN in patients with CAD and with lower erythrocyte sedimentation rate, could reflect this finding as autonomic imbalance contributes to or is affected by increased inflammation.

In the same manner, heart failure is associated with more severe ANS dysfunction[30], with sympathetic and renin-angiotensin-aldosterone hyperactivity. This could prevent greater improvements in HRV compared to patients with a normal systolic function. This result should not keep us from pushing because there is evidence that the reduction of sympathetic activity by exercise training in heart failure patients is associated with a better clinical outcome[31,32].

Tobacco use is associated with autonomic imbalance and decreased HRV[33,34] mainly due to nicotine exposure with catecholamine release and augmented sympathetic outflow[35]. In this sense, smoking cessation leads to an increase of HRV[36]. In our cohort of patients, smoking cessation was an independent predictor of HRR improvement. The mechanism behind this fact is the same for HRV, since rapid decline in HR following exercise is largely due to parasympathetic restoration and both, exercise and smoking cessation in chronic smokers, increase vagal tone.

Medication may alter ANS function, particularly beta blockers, with clinical benefits[37]. As we mentioned before, all the patients were on beta blockers, with a stable dose during CR, thus the positive effects on ANS must have come from exercise training[38].

The main finding of this work was that CR programme generated a positive effect on ANS, mainly in those with autonomic dysfunction. CAD patients, in sinus rhythm, with lower systemic inflammation and with normal or mild systolic dysfunction were more likely to improve ANS function.

LIMITATIONS

This was a retrospective analysis of consecutively admitted CAD patients in sinus rhythm and the results reflect a single-centre experience without control group.

Smoking status was assessed by self-reporting rather than a biochemical method, in the group of smokers, the burden of tobacco use was not assessed. This fact could have clinical relevance because heavier smokers have greater autonomic dysfunction and isolated nicotine use deleteriously affects HRV[39].

CONCLUSION

Cardiac rehabilitation induced a positive modulation of the autonomic nervous system function in coronary artery disease patients. This benefit was more pronounced in patients with autonomic nervous system dysfunction, objectively demonstrated by SDNN inferior to 100 ms and abnormal heart rate recovery, and also with normal LV function to mild left ventricular systolic dysfunction and with lower erythrocyte sedimentation rate.

CONFLICT OF INTEREST: none.

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