Physical Medicine and Rehabilitation - International

Open Access

Austin Publishing Group

Special Article - Cardiac Rehabilitation

Improvement of Chronotropic Incompetence after a Rehabilitation Program in Obese Patients with Coronary Artery Disease Treated with Beta-Blockers: A Practice Level Study

Gondoni LA[1]*, Bertone G[1], Titon AM[1], Nibbio F[1] and Montano M[2]

[1]IRCCS Istituto Auxologico Italiano, Unit of Cardiac Rehabilitation, Ospedale San Giuseppe, Piancavallo (VB), Italy

[2]Ospedale Castelli, Department of Cardiology, Verbania, Italy

***Corresponding author:** Luca Alessandro Gondoni, IRCCS Istituto Auxologico Italiano, Unit of Cardiac Rehabilitation, Ospedale San Giuseppe, Piancavallo (VB), Italy

Received: August 10, 2018; **Accepted:** September 18, 2018; **Published:** September 25, 2018

Abstract

Background: Resting and peak exercise heart rate (HR) predict survival in various settings of patients; the same is true for chronotropic index (CI) which is a marker for all-cause mortality. We do not have data on the effect of rehabilitation on CI in obese patients affected with coronary artery disease (CAD) and treated with beta-blockers, who represent the majority of the patients we run into in everyday practice. A cardiac rehabilitation program which includes exercise and weight loss improves autonomic balance and therefore could improve CI during an exercise stress test.

Methods: We studied 432 consecutive white obese patients (123 females – 29%), aged 59.9 ± 9.0 years, affected with clinically stable CAD, treated with beta-blockers. All the patients underwent a short (23 ± 4 days) in hospital rehabilitation program consisting, among other interventions, of physical activity and diet. A treadmill exercise stress test was performed at the beginning and the end of the hospital stay.

Results: By the end of the program besides an improvement in BMI and attained METs, all HR variables were significantly improved: resting HR decreased from 69 ± 11 to 65 ± 11 beats/min; peak HR increased from 112 ± 17 to 115 ± 19 and CI increased from 0.47 ± 0.16 to 0.52 ± 0.17 (P< 0.001 for each comparison).

Conclusions: Weight loss and exercise training improve resting and peak HR and CI in obese patients affected with CAD and permanently treated with beta-blockers.

Keywords: Chronotropic index; Coronary artery disease; BMI; Beta-blockers

Introduction

Heart rate (HR) both at rest and as a response to exercise is a powerful predictor of survival in various settings of patients: a high resting HR independently predicts mortality in patients with coronary artery disease (CAD) as well as in healthy subjects [1-3]. Also a blunted increase in HR and, consequently, an inadequate chronotropic index (CI) during exercise are both strong predictors for sudden death in healthy subjects [2,3]; among patients with coronary disease and with congestive heart failure, chronotropic incompetence independently predicts all-cause mortality [4,5]. Considering the prognostic values of HR parameters, improving the behavior of HR during an exercise test by reducing resting values and increasing peak HR and CI should be a target of rehabilitation programs, particularly in obese patients who already have a low CI and peak HR which both contribute to their reduced exercise tolerance [6].

Obesity is a worldwide problem and its prevalence has reached epidemic proportions, particularly in patients affected with CAD. Cardiometabolic rehabilitation increases exercise tolerance and favors weight loss, reducing many parameters of cardiovascular risk [7]. A benefit of physical training and weight loss in obese subjects on heart rate recovery after exercising, which is another powerful marker for survival, has already been documented [8]. Nonetheless we have no data on CI behavior in obese patients affected with CAD. This is particularly true if we consider patients treated with beta-blockers, thus making it difficult to translate results into clinical practice, since beta-blockers remain a cornerstone of treatment in CAD also in obese subjects who have by themselves a reduced CI.

We have studied obese patients with documented CAD on chronic beta-blocker therapy, considering that also in this subset of patients HR parameters keep their clinical meaning [9]: we hypothesized that weight loss and physical training, that are both core components of cardiac rehabilitation, would ameliorate autonomic balance and therefore improve CI during an exercise stress test also in that peculiar setting of patients.

Patients and Methods

We studied 432 consecutive white obese patients (123 females –

Citation: Gondoni LA, Bertone G, Titon AM, Nibbio F and Montano M. Improvement of Chronotropic Incompetence after a Rehabilitation Program in Obese Patients with Coronary Artery Disease Treated with Beta-Blockers: A Practice Level Study. Phys Med Rehabil Int. 2018; 5(4): 1153.

Table 1: Differences in HR variables by sex, diabetes and obesity.

Variable	Females	Males	P	Diabetics	Non diabetics	P	Mild Obesity	Moderate Obesity	Severe Obesity	P ANOVA
Resting HR	70 ± 11	69 ± 11	0.376	71 ± 12	68 ± 11	0.011	69 ± 12	68 ± 12	73 ± 10	0.001
Peak HR	109 ± 17	113 ± 17	0.029	111 ± 16	113 ± 18	0.241	112 ± 18	111 ± 17	114 ± 17	0.408
CI	0.45 ± 0.17	0.49 ± 0.15	0.025	0.46 ± 0.16	0.49 ± 0.16	0.107	0.48 ± 0.16	0.47 ± 0.16	0.47 ± 0.16	0.636
CI Keteyian	0.74 ± 0.28	0.81 ± 0.25	0.014	0.76 ± .026	0.81 ± 0.26	0.049	0.80 ± 0.26	0.78 ± 0.26	0.78 ± 0.26	0.699

Table 2: Differences baseline variables with respect to ejection fraction.

Variable	FE < 40%	FE 40-54%	FE ≥ 55%	P
Age	61.1 ± 8.2	60.0 ± 8.7	59.9 ± 9.4	0.516
BMI	37.9 ± 5.2	37.5 ± 4.8	37.8 ± 4.7	0.777
METs absolute	6.0 ± 1.9	6.8 ± 2.3	6.8 ± 2.4	0.087
METS % of predicted[1]	70 ± 21%	79 ± 23%	82 ± 25%	0.004
Resting HR	72 ± 12	69 ± 12	69 ± 11	0.226
Peak HR	111 ± 18	112 ± 18	113 ± 17	0.764
CI	0.44 ± 0.15	0.48 ± 0.17	0.48 ± 0.15	0.336
CI Keteyian	0.73 ± 0.26	0.79 ± 0.27	0.80 ± 0.25	0.247

BMI: Body Mass Index; Mets: Metabolic Equivalents; HR: Heart Rate; CI: Chronotropic Index; HRR: Heart Rate Recovery

[1]Post hoc testing of the differences among the three groups showed that only the worst EF group was associated with a reduced exercise tolerance.

29%), affected with CAD and chronically treated with beta-blockers. The patients signed an informed consent before participation in the rehabilitation program and before doing the exercise test.

Body weight was measured in the morning after overnight fasting and after voiding: it was checked at admission and at the end of the program. BMI was calculated dividing weight (in kilograms) by height^2 (in meters). Obesity was defined as a body mass index (BMI) 30kg/m^2 and was subdivided in three categories: mild obesity 30-35, moderate obesity 35-40 and severe obesity > 40kg/m^2 according to the current classification. For the purpose of this study, CAD was defined as a documented history of at least one of the following: myocardial infarction, coronary artery by-pass, coronary angioplasty/stenting. Every patient was in a clinically stable condition: we excluded patients with recent (less than 4 weeks) myocardial infarction or coronary intervention. All patients were in sinus rhythm and none had a pacemaker of any kind. We also excluded patients who took other drugs that might interfere with HR such as verapamil, diltiazem, digoxin, ivabradine, and all antiarrhythmic agents. Treatment with beta-blockers was maintained throughout the rehabilitation period.

The methodology of the program represents the routine at our institution and consists, beyond psychological support and patients' education, of a short in-hospital program of low-calorie diet and physical training. Exercise stress test was conducted on the second day of the hospital stay and was repeated again at the end of the program, after a mean period of 23 ± 4 days. Patients took their usual medications, including beta-blockers, and had a light breakfast before the test. We utilized a GE series 2000 motorized treadmill with a GE Case ECG instrumentation. We used an individualized ramp protocol that has been described before [10] and measured the intensity of exercise using metabolic equivalents (METs). Resting HR was calculated on the ECG strip in the standing position before the beginning of exercise, peak HR was calculated when effort was stopped and recovery began, and CI was calculated according to the following formula: CI = (Attained maximal HR – Resting HR) / (Predicted maximal HR – Resting HR). Predicted maximal HR was calculated by the formula 220 – age. We also used the formula proposed by Keteyian et al [11] for patients on beta-blocker treatment, which calculates predicted peak HR using the following correction: predicted peak HR = 119 + (resting HR/2) – (age/2). All our patients exercised on a treadmill and therefore we excluded the factor that corrects when a bicycle ergometer is used. Exercise tolerance was considered both as an absolute value and as the ratio between attained METs and predicted value according to the equation we previously published [10]. Each patients underwent an echocardiographic study to measure ejection fraction (EF).

Physical activity program: the intensity of the program was determined on the basis of the baseline exercise test. It entailed daily sessions (6 days a week) of aerobic activity which included 30 minute sessions of cycle-ergometer, walking at low speed for about 45 minutes (3-4 METs), and 30 minutes of low intensity strength exercise. All patients underwent a personal interview with an experienced physical trainer to individualize their activity program which was subsequently titrated to the improvement achieved.

Diet: resting energy expenditure (REE) was estimated by the Harris Benedict equation [12]. Diet was assigned by a dietician after a personal interview with the patient and mean caloric intake was set at around 85% of REE with a mean caloric deficit of 244 ± 220 kcal/day. Diet derived 50% of energy from carbohydrates, 30% from lipids, and 20% from proteins.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) and categorical variables are presented as number and percentage. Study variables were resting HR, peak HR, and CI calculated according to both formulae as stated above. We also considered BMI and attained METs. T test for paired variables was executed to examine differences in the study variables before and after the program. To discriminate whether different categories of patients had different level of improvement we used a T test for unpaired data or one way ANOVA when the categories were more than two. As a post hoc test we used LSD. When appropriated a Chi-square test was used. We considered the improvement as expressed by the percentage variation in each of the study variables with the formula % = (Final - Baseline)/Baseline.

Data were analyzed with the SPSS V.23.0 package (SPSS, Chicago, Illinois, USA).

Results

The mean age of our patients was 59.9 ± 9.0 years (range 36.9 – 79.7). Mean BMI was 37.7 ± 4.8 kg/m^2 (range 30.0 – 54.4); 144

Table 3: Improvement in BMI, attained METs and HR variables after the program.

Variable	Before	After	Difference	95% Confidence Interval	P
BMI	37.7 ± 4.8	36.4 ± 4.6	-1.2 ± 0.6	-1.2 / -1.3	< 0.001
METs	6.7 ± 2.3	7.8 ± 2.6	1.1 ± 1.1	1.0 / 1.2	< 0.001
METS % of predicted	79.6 ± 23.7%	92.6 ± 25.5%	13.1 ± 12.4%	12 / 14	< 0.001
Resting HR	69 ± 11	65 ± 11	-4 ± 11	-3 / -5	< 0.001
Peak HR	112 ± 17	115 ± 19	3 ± 14	1 / 4	< 0.001
CI	0.47 ± 0.16	0.52 ± 0.17	0.05 ± 0.13	0.04 / 0.06	< 0.001
CI Keteyian	0.79 ± 0.26	0.88 ± 0.29	0.08 ± 0.21	0.07 / 0.11	< 0.001

BMI: Body Mass Index; Mets: Metabolic Equivalents; HR: Heart Rate; CI: Chronotropic Index

Table 4: % improvement in HR variables by age, BMI, diabetes.

Variable	Diabetics	Non diabetics	P	Mild Obesity	Moderate Obesity	Severe Obesity	P ANOVA	Age tertile 1	Age tertile 2	Age tertile 3	P ANOVA
Resting HR	-4±16%	-4±16%	0.719	-4±13%	-3±19%	-6±13%	0.174	-3±16%	-4±17%	-5±16%	0.851
Peak HR	3±13%	3±13%	0.582	4±13%	4±15%	1±11%	0.178	3±13%	4±12%	2±14%	0.367
CI	16.3±3.8%	14.8±3.4%	0.676	17±38%	17±38%	12±28%	0.423	9.9±30.9%	18.3±29.7%	18.1±44.5%	0.079
CI Keteyian	17.2±3.8%	15.4±3.4%	0.593	17±37%	18±38%	13±28%	0.487	10.5±30.7%	19.1±30.0%	18.8±43.3%	0.064

patients (33%) had mild obesity, while 171 (40%) had moderate obesity and 117 (27%) had severe obesity. As stated, every patient had stable CAD; 336 patients (78%) also had hypertension, 78 (18%) a history of heart failure, and 185 (43%) had diabetes.

Mean EF was 53 ± 10% (range 20 – 79%): 52 patients (12%) had severely depressed EF (<40%), 173 (40%) had mildly depressed EF (40-55%) and 205 (48%) had normal EF (>55%).

The role of several variables on baseline data was explored. Women had the same resting HR, but lower peak HR and CI (table 1). Women were also slightly older (61.7 ± 8.6 vs 59.2 ± 9.0 years; P = 0.007), had higher BMI (38.7 ± 4.8 vs 37.2 ± 4.7 Kg/m^2; P = 0.003) and a lower prevalence of diabetes (34% vs 46%; P = 0.024) as compared to men. Women also had a lower exercise tolerance if considered as an absolute value, but not if the ratio between attained and predicted METs, which takes into account sex, was evaluated.

Diabetics instead had significantly higher resting HR and a trend towards a lower peak HR and CI, but only the CI value corrected by the Keteyian formula reached statistical significance (Table 1). Moreover diabetic patients were older as compared to non-diabetics patients (61.4 ± 8.0 vs 58.8 ± 9.5 years; P = 0.006), they had lower baseline exercise tolerance (6.4 ± 2.2 vs 6.9 ± 2.4 METs; P = 0.029), but the difference disappeared after controlling for age.

The role of BMI on heart rate variables was evident only on resting HR which was higher in the severely obese patients, while CI and peak HR did not differ significantly (Table 1). A significant trend in exercise tolerance, both as absolute and relative values, was evident with respect to obesity severity: 7.4 ± 2.3 METs or 88 ± 24% for mild obese vs 6.7 ± 2.4 METs or 79 ± 22% for moderate obese vs 5.8 ± 2.0 METs or 70 ± 21% for severely obese patients (P ANOVA < 0.001).

EF had no effects on HR variables and had only a borderline effect on the absolute value of attained METs which reached statistical significance if the ratio between attained and predicted value was considered: at post hoc analysis the patients with the more severely depressed EF exercised less than the other groups (Table 2).

By the end of the program BMI, attained METs and all HR rate variables improved significantly (Table 3). No significant correlation was found among the reduction in BMI and the improvement of HR variables.

The normal value for CI in patients treated with beta-blockers has been set at ≥ 0.62 [11]. In our population the number of patients who fell within such normal limits was 83 (19%) at baseline and increased to 138 (32%) at the end of the program. If we considered the Keteyian correction, setting the normal limit at ≥ 0.80 as for patients not taking beta-blockers, the values were respectively 214 (43) and 248 (57%).

Diabetic patients, while losing significantly less weight than non-diabetics, showed the same improvement as non-diabetic patients in each of the study variables; also age did not exert any significant effect on the results of the program (Table 4), even if there was a non-significant trend towards a better improvement in the CI of the elderly subset of patients.

Discussion

The main finding of our study is that in obese patients affected with CAD chronically treated with beta-blockers physical training and weight loss cause a significant improvement in chronotropic incompetence measured at an exercise stress test: even if the improvements are modest as absolute values, the percentage variation is not trivial. To the best of our knowledge, this is the first study that demonstrates an improvement in chronotropic incompetence in obese patients treated with beta-blockers who represent indeed the majority of CAD patients.

Heart rate control during exercise conditions is a complex physiological process: the initial increase is mainly caused by a withdrawal in parasympathetic inhibition which is followed by a rise in sympathetic tone. Training is known to increase resting vagal tone and therefore to act mainly on resting HR; vagal tone is not affected by treatment with beta-blockers, while sympathetic tone, which on the contrary is blunted by beta-blockers, has a major impact in determining both peak and resting HR and, as a consequence,

on CI. HR increases during exercise as a physiologic response to the boost in metabolic demand that exercise itself causes and is the main contributor to the physiological increase in oxygen [13]: therefore an inappropriate response is one of the causes of a reduced exercise tolerance, particularly in those patients with left ventricular dysfunction. The impaired chronotropic response has important implications both for quality of life and prognosis: its reversal might therefore have a clinically meaningful effect. The number of patients who normalized their CI almost doubled, albeit remaining quite low, probably as a consequence of the altered autonomic status and the reduced exercise tolerance which is characteristic to obese patients.

Importantly, both patients with diabetes and the elderly subset of subjects had an improvement in HR variables that was almost identical to non-diabetics and younger ones. Diabetes is characterized by a sympathetic over activity and a low parasympathetic tone: such an autonomic dysfunction is a critical risk factor that contributes to the increased cardiovascular morbidity and mortality associated with obesity and diabetes. Physical exercise can partially reverse it by restoring a better autonomic modulation [14] and weight loss in itself, as it happens after bariatric surgery, is capable to induce an improvement in exercise capacity and HR variables [15,16].

We are convinced that an incremental value of our study lies in the fact that it is not a randomized study, but rather it describes a standard rehabilitation program in a non-selected population in which exclusion criteria were limited to the indispensable requirements in order to avoid major biases: thus our results can more easily be interpreted and handed over in a real world population. Also the lack of a control group is somehow necessary, being the consequence of a methodological problem in rehabilitation research: the efficacy of cardiac rehabilitation and the benefits of weight loss in obese subjects are indeed well known [17]; as a consequence, the design of randomized controlled trials in such settings trial poses several ethical problems and in our opinion we do not have the possibility to identify a true non-intervention group: if obese patients with CAD participate in a rehabilitation program they must undergo exercise and dieting and only a choice among different rehabilitation protocols can be feasible, but we already know that the differences in such cases are small [18,19].

Whether the improvements that we have demonstrated have also an impact on long term survival has to be tested in follow-up studies. Anyway, once again, for the same reasons stated above, it should be considered unethical to design a randomized controlled trial with a non-intervention group and strict exclusion criteria [20,21] and only an observational longitudinal study could possibly be the instrument to test the long term effects of the improvement in CI that we demonstrated.

References

1. Diaz A, Bourassa AG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005; 26: 967-974.
2. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. New Engl J Med. 2005; 352: 1951-1958.
3. Savonen KP, Lakka TA, Laukkanen JA, Halonen PM, Rauramaa TH, Salonen JT, et al. Heart rate response during exercise test and cardiovascular mortality in middle-aged men. Eur Heart J. 2006; 27: 582-588.
4. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999; 281: 524-529.
5. Magrì D, Corrà U, Di Lenarda A, Cattadori G, Maruotti A, Iorio A, et al. Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. Eur J Heart Fail. 2014; 16: 201-209.
6. Gondoni LA, Titon AM, Nibbio F, Augello G, Caetani G, Liuzzi A. Heart rate behavior during an exercise stress test in obese patients. Nutr Metab Cardiovasc Dis. 2009; 19: 170-176.
7. Gondoni LA, Titon AM, Nibbio F, Caetani G, Augello G, Mian O, et al. Short-term effects of a hypocaloric diet and a physical activity programme on weight loss and exercise capacity in obese subjects with chronic ischaemic heart disease: a study in everyday practice. Acta Cardiol. 2008; 63: 153-159.
8. Brinkworth GD, Noakes M, Buckley JD, Clifton PM. Weight loss improves heart rate recovery in overweight and obese men with features of the metabolic syndrome. Am Heart J. 2006; 152: 693.e1–693.e6.
9. Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta-blockers (metoprolol or atenolol). Am J Cardiol. 2005; 96: 1328-1333.
10. Gondoni LA, Liuzzi A, Titon AM, Taronna O, Nibbio F, Ferrari P, et al. A simple tool to predict exercise capacity of obese patients with ischemic heart disease. Heart. 2006; 92: 899-904.
11. Keteyian SJ, Kitzman D, Zannad F, Landzberg J, Arnold JM, Brubaker P, et al. Predicting maximal HR in heart failure patients on β-blockade therapy. Med Sci Sport Exerc. 2012; 44: 371-376.
12. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC, USA: Carnegie Institution of Washington. 1919.
13. Higginbotham MB, Morris KG, Sanders Williams R, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal upright exercise in normal man. Circ Res. 1986; 58: 281-291.
14. Voulgari C, Pagoni S, Vinik A, Poirier P. Exercise improves cardiac autonomic function in obesity and diabetes. Metabolism. 2013; 62: 609-621.
15. Serès L, Lopez-Ayerbe J, Coll R, Rodriguez O, Vila J, Formiguera X, et al. Increased exercise capacity after surgically induced weight loss in morbid obesity. Obesity. 2006; 14: 273-279.
16. Wasmund SL, Owan T, Yanowitz FG, Adams TD, Hunt SC, Hamdan MH, et al. Improved heart rate recovery after marked weight loss induced by gastric bypass surgery: two-year follow up in the Utah Obesity Study. Heart Rhythm. 2011; 8: 84-90.
17. Sandesara PB, Lambert CT, Gordon NF, Fletcher GF, Franklin BA, Wenger NK, et al. Cardiac rehabilitation and risk reduction. Time to "Rebrand and reinvigorate". J Am Coll Cardiol. 2015; 65: 389-395.
18. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015; 102: 780-790.
19. Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. Lancet. 2016; 387: 1947-1956.
20. Gondoni LA, Liuzzi A. Diet and Physical Activity Interventions in Severely Obese Adults. JAMA. 2011; 305: 563.
21. Capodaglio P., Lafortuna C, Petroni ML, Salvadori A, Gondoni L, Castelnuovo G, et al. Rationale for hospital-based rehabilitation in obesity with comorbidities. Eur J Phys Rehabil Med. 2013; 49: 399-417.