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A patient-centered multidisciplinary cardiac rehabilitation program improves glycemic control and functional outcome in coronary artery disease after percutaneous and surgical revascularization

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A patient-centered multidisciplinary cardiac rehabilitation program improves glycemic control and functional outcome in coronary artery disease after percutaneous and surgical revascularization

Patient-centered cardiac rehabilitation program improves outcome after ACS

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ABSTRACT

Background: Cardiac rehabilitation (CR) is strongly associated with all-cause mortality reduction in patients with coronary artery disease (CAD). The impact of CR on pathological risk factors, such as impaired glucose tolerance (IGT), and functional recovery remains under debate. The aim of the present study is to determine whether CR has a positive effect on physical exercise improvement and on pathological risk factors in IGT and diabetic patients with CAD.

Methods: One hundred and seventy-one consecutive patients participating in a 3-month CR from January 2014 to June 2015 were enrolled. The primary endpoint was defined as an improvement of peak workload and VO2-peak; glycated hemoglobin (HbA1c) reduction was considered as a secondary endpoint.

Results: Euglycemic patients presented a significant improvement in peak workload compared to diabetic patients (from 5.75 ± 1.45 to 6.65 ± 1.84 METs, p = 0.018 vs. $4.8 \pm$

0.8 to 4.9 ± 1.4 METs). VO2-peak improved in euglycemic patients (VO2-peak from 19.3 ± 5.3 mL/min/kg to 22.5 ± 5.9, p = 0.003), while diabetic patients did not present a statistically significant trend (VO2-peak from 16.9 ± 4.4 mL/min/kg to 18.0 ± 3.8, p < 0.056). Diabetic patients have benefited more in terms of blood glucose control compared to IGT patients (HbA1c from 7.7 ± 1.0 to 7.4 ± 1.1 compared to 5.6 ± 0.4 to 5.9 ± 0.5, p = 0.02, respectively).

Conclusions: A multidisciplinary CR program improves physical functional capacity in CAD setting, particularly in euglycemic patients. IGT patients as well as diabetic patients may benefit from a CR program, but long-term outcome needs to be clarified in larger studies.

Key words: cardiac rehabilitation, coronary artery disease, diabetes mellitus, reduced glucose tolerance, cardiopulmonary test

Introduction

Cardiovascular disease and acute coronary syndrome (ACS) represent a major source of morbidity and mortality in Western countries [1]. Cardiac rehabilitation (CR) has been strongly associated with a reduction in all-cause mortality in patients with coronary artery disease (CAD), hospital readmissions, costs and improvement in exercise capacity, quality of life and psychological well-being [2–5]. Therefore, CR is currently a mainstay of post-acute care strategy and is recommended by international guidelines for stable CAD (Class I, Level A). A multi-factorial intervention including patient assessment, physical activity/diet/nutritional counselling, exercise training, risk factor control, patient education, psychosocial management, and vocational advice are also recommended for patients with ST-elevation acute myocardial infarction (Class I, Level B), and non ST-elevation myocardial infarction (Class IIa, Level A) [6, 7]. Exercise capacity, measured by VO2-peak, is an independent predictor of all-cause and cardiovascular mortality in patients with CAD [8, 9]. Diabetic patients are known to be at higher risk for CAD, with a worse prognosis after a myocardial infarction compared to non-diabetic patients [10, 11]. Previous studies have shown that CR is less effective in these patients, probably due to impaired glycemic control [12]. Less is known about the value of impaired glucose tolerance (IGT) as a predictor of cardiovascular events in the long-term, however this condition seems to be associated with lower functional recovery [13, 14]. Recently, a positive association between IGT and left ventricular diastolic dysfunction was found in middle-age adults without left ventricular

systolic impairment or valvular disease, even after correction for confounding factors [15]. The cardiopulmonary exercise testing (CPET) is commonly performed in patients with CAD to identify post-infarct residual ischemia and to monitor the progress of CR [16, 17]. The aim of the present study is to determine whether CR has a positive effect on exercise capacity and risk factor control in IGT and diabetic patients with CAD.

Methods

One hundred and seventy-one consecutive patients referred to Cardiocentro Ticino (Lugano, Switzerland) for CR, from January 2014 to June 2015, were enrolled in the study. Patients with severe renal failure (as defined by RIFLE classification — Risk, Injury, Failure, Loss of kidney function and End-stage renal disease based on creatinine clearance and urinary output) [18], severe peripheral arterial disease, severe respiratory disease or those simply unable to perform exercise training were excluded. Diabetes was diagnosed by plasma fasting glucose > 126 mg/dL (i.e. > 7.0 mmol/L) or by glycated hemoglobin (HbA1c) > 6.5%. A tri-weekly 2-h session of a comprehensive multidisciplinary CR program began on hemodynamically stable patients and continued for three months. The CR team consisted of physiotherapists, psychologists, nutritionists and an experienced cardiologist in cardiovascular rehabilitation. Each session included one or more group-based therapies, such as education about cardiovascular risk factors, dietary suggestions, and physiotherapy as well as exercise and stress management. Exercise sessions of aerobic exercise lasting 30 min,   including a warm-up and a cool-down activity. The intensity of exercise was prescribed individually, based on a target heart rate < 85% of the theoretical threshold. Demographic information, anthropometric parameters, medical history, ACS type, cardiovascular risk factors, medications as well as laboratory values were collected at baseline and after completing the CR program (at least > 75% of sessions). A CPET was performed at baseline and at the end of the CR program and was supervised by an experienced cardiologist. This ergometric CPET was conducted with variable work loads of 10 to 25 Watts every 1 or 2 min (incremental protocol), according to a patient's individual functional autonomy. A measurement of patient cardiopulmonary function, such as maximal metabolic equivalents (METs), peak workload and maximal oxygen consumption (VO2-peak), were collected at baseline and at the end of the CR program.

Statistical analysis

Variables were expressed as means ± standard deviation or percentage as appropriate. Comparisons between groups were performed using the two-tailed Student t-test or χ^2 test as appropriate. Correlation coefficients were determined by linear regression analysis and statistical significance was determined with the Fisher and Yates test. Multivariable analyses were performed by stepwise linear regression or by stepwise logistic regression as appropriate. A p-value < 0.05 was considered to be statistically significant. Statistical analysis was performed using the SPSS software (SPSS 22.0 Inc., Chicago IL, USA).

Results

Out of 171 patients enrolled in the study, 148 (86.5%) completed the CR program; 87 (50.9%) patients presented ACS in the prior4 weeks and 108 (63.1%) underwent a percutaneous transluminal coronary angioplasty (PTCA). After 1 week, 23 (13.4%) patients dropped out the CR program and another 4 patients were excluded from the analysis because of attendance of less than 75% of the sessions (less than 28 f the 36 sessions). Out of 144 patients who completed the CR program, 34 (23.6%) patients were already known to have diabetes; 3 (2.1%) patients were newly diagnosed. Patients with a plasma fasting glucose between 100 and 126 mg/dL (i.e. 5.56 mmol/L and 7.0 mmol/L), independent of their history, were classified as IGT patients; of these 47 (32.6%) were newly diagnosed. The baseline characteristics of the 171 patients, were divided in three groups according to their baseline fasting glucose and enrolled in the study and are summarized in Table 1.

Effects on exercise capacity based on glucose control

Exercise capacity pre- and post-CR expressed by CPET parameters is summarized in Table 2. All groups showed significant intra-group improvement (Fig. 1) considering workload peak and VO2-peak (except IGT patients). Euglycemic patients benefited the most in terms of exercise capacity improvement (5.7 ± 1.4 to 6.6 ± 1.8 METs, p = 0.018). IGT patients presented a lower functional capacity recovery when compared to euglycemic patients (5.9 ± 1.9 to 6.3 ± 1.8 METs, p = 0.413) as well as diabetic patients (4.8 ± 0.8 to 4.9 ± 1.4, p = 0.072).

A significant improvement in VO2-peak after completing CR was found in euglycemic patients (VO2-peak from 19.3 ± 5.3 mL/min/kg to 22.5 ± 5.9 mL/min/kg, p = 0.003) and also in this case, IGT patients showed less benefit compared to euglycemic patients (VO2-peak from 20.2 ± 6.4 mL/min/kg to 21.5 ± 7.0 mL/min/kg, p = 0.42). Diabetic patients presented only a positive trend in VO2-peak compared to IGT (VO2-peak 17.0 ± 3.8

mL/min/kg vs. 18.1 ± 4.4 mL/min/kg, p = 0.056). IGT patients presented with the most significant benefit in terms of fasting glucose reduction, in the absence of hypoglycemic therapy, compared to diabetic patients (plasma fasting glucose 6.5 ± 0.5 mmol/L to 6.2 ± 0.9 mmol/L vs. 8.1 ± 1.8 mmol/L to 8.2 ± 1.9 mmol/L, p = 0.002). Diabetic patients, on the other hand, showed a more significant reduction of HbA1c levels compared to IGT patients (HbA1c 7.7 ± 1.1% to 7.5 ± 1.2% vs. 5.6 ± 0.4% to 6.0 ± 0.5%, p = 0.002). Finally, a trend showing an inverse correlation was found between baseline fasting glucose levels and ΔVO2-peak (ΔVO2-peak = 6.419925–0.721243*fasting glucose, p = 0.11, Fig. 2).

Discussion

In this study, results of a comprehensive CR program for CAD patients from a single center experience are presented (Cardiocentro Ticino, Lugano, Switzerland). In the current population, 13.4% of patients quit the CR program after 1 week. This dropout rate is in line with the data previously reported in the literature [19]. In a big prospective study, including more than 25,000 patients with at least one vessel CAD, diabetic patients were more likely to leave the CR program (odds ratio [OR] 0.65, 95% confidence interval [CI] 0.59–0.72), and, despite being less referred, women experienced a greater relative mortality benefit compared to men [20].

Effects of CR programs on cardiovascular risk factors

Exercise capacity measured by VO2-peak represents a strong predictor of survival in patients with CAD and is positively related to improvement in terms of morbidity [21].

High-intensity interval training protocols have been developed and have been shown to lead to a significant increase in functional capacity compared to moderate continuous training [22]. International Guidelines recommend CR programs including a multimodal behavioral intervention for all patients with established CAD [6, 7].

Exercise is associated with improvements of typical cardiovascular risk factor control such as obesity, diabetes mellitus and hypertension [23]. In the present population, a reduction in weight as well as in waist circumference in all patients was found, independent of glycemic status, although these results were not statistically significant as reported in other previous studies published [24]. Moreover, CR is associated with an increase of muscular mass; therefore, weight loss may not reflect by itself a reduction in cardiovascular risk. An increase in oxygen peak consumption or improvement in glycemic control thus represent more useful indicators.

Effects of CR programs based on glycemic status

The combination of aerobic and resistance training has been shown to be highly effective in reducing cardiovascular risk factors in patients with type 2 diabetes mellitus and is currently recommended by the American College of Sports Medicine and American Heart Association [25, 26]. In the analyses, it was found that IGT patients presented a more significant reduction in plasma fasting glucose compared to diabetic patients. On the other hand, diabetic patients showed a more significant reduction of HbA1c levels, compared to IGT patients. Based on these results, it can be extrapolated that these patients could benefit, in terms of glycemic control, from a longer CR program.

The role of CR as long-term therapy to reduce cardiovascular risk factors after ACS is well established. In a prospective study including 846 patients treated with aorto-coronary by-pass, CR attendance was associated with a significant reduction of 10-year all-cause mortality and CR program completion was the most important indicator for survival [27]. However, no differences in mortality according to glycemic status were found.

In *in vitro* studies, hyperglycemia has been shown to lead to oxidative stress and thus, indirectly, to increase myocyte apoptosis, both in chronic and in acute settings [28, 29]. In the DARE study, a prospective multicenter study, 64 patients with diabetes mellitus type 2 were enrolled in a CR program after ACS. Patients were randomized according to baseline diabetes therapy; patients with better glycemic control, as measured by fructosamine levels, the parameter of short-term glycemic control showed higher values of VO2-peak at the end of CR [19]. In another prospective study including 682 patients undergoing CR after ACS, diabetic subjects presented a lower functional capacity at baseline compared to non-diabetics. Nevertheless, diabetics patients presented a significant improvement, expressed in METs and exercise duration, similar to those achieved by non-diabetic patients [30]. These findings were confirmed in another study including heart failure patients [31]. In the current study, it was also found that patients with diabetes have a lower functional capacity at baseline, with an improvement in functional capacity, expressed in terms of both higher peak workload (METs) and VO2-peak values at the end of the CR program when compared to IGT patients. Euglycemic patients, on the contrary, significantly improved both these parameters compared to diabetic patients.

Data from the Italian SurveY on carDiac rEhabilitation (ISYDE-2008) including 2281 patients referred to CR showed that patients with diabetes had more comorbidities and 23% of them were not able to perform any physical performance testing at all. The authors concluded

that this finding might have prognostic relevance. A bias in the study involving diabetic patients undergoing CR has thus to be considered, as these patients may have been directly excluded from enrollment in CR programs [32].

In the present study, euglycemic patients benefited the most from the CR program. IGT patients, however, presented a significant improvement of glycemic control compared to diabetic patients in terms of plasma fasting glucose. Diabetic patients, on the other hand, showed a statistically significant reduction of HbA1c. Taken together, these data suggest that improvement in glycemic control during CR may contribute to optimize functional recovery expressed in terms of workload- and VO2-peak, independently from other factors. These improvements are probably due to CR itself, and were independent of underlying therapy for diabetes. Several studies, however, failed to demonstrate the effectiveness of CR in diabetic patients [33, 34], although, according to some other authors, CR should be effective for these patients as well [35]. However, the discrepancies in these studies may be related to the heterogeneity of patients considered. In the current study, it was found that fasting glucose at baseline inversely correlated with VO2-peak improvement and this finding is in line with previously published data [12, 36]. Poor glycemic control seems to have unfavorable effects on cardiomyocytes and muscular cells, promoting overproduction of reactive oxygen species, alterations of myocardial endo-plasmatic reticulum, dysfunction of calcium metabolism and impairment of mitochondria metabolism [29, 37–39]. On the other hand, good glycemic control during CR may improve the VO2-peak [17] and may play a key role for a better long-term prognosis as well.

Limitations of the study

This retrospective analysis, as well as the lack of a control group represent a limitation of this study, it is also burdened by a small number of patients, all Caucasian. Larger prospective studies are needed to better clarify the role of CR in diabetic patients.

Conclusions

This single-center experience showed how a multidisciplinary CR program provides better outcomes in terms of exercise capacity for euglycemic patients compared to IGT and diabetics patients. These latter patients could benefit from a longer CR program, overall in terms of glycemic control, independent from hypoglycemic therapies. The efficacy of CR in diabetic patients needs to be clarified in larger and prospective studies.

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Table 1. Main characteristics of cardiac rehabilitation (CR) patients according to glycemic status.

	Euglycemic (glycemic < 5.6 mmol/L) (n = 88)	IGT (glycemic 5.6–7.0 mmol/L) (n = 59)	Diabetics (glycemic > 7.0 mmol/L) (n = 24)
Age	60,45	63,35	69,30
Male	53	66	24
Familial history of CHD	25	23	4
Hypertension	32	42	20
Dyslipidemia	36	40	11
Diabetes	1	12	21
Smoking	35	38	6
Statin therapy	56	61	21
ACEI	40	41	19
Beta-blockers	59	68	17
Acetylsalicylic acid	64	68	24
Stable angina	28	20	9
Unstable angina	3	2	0
NSTEMI	18	4	4
STEMI	25	22	9
PTCA	55	40	13
CABG (also previous)	23	12	12
Waist > 88 or > 102 cm	31	33	17
Weight > 60 or > 70 kg	50	66	23
ΔGlucose	−0.16 ± 0.46 (p = 0.25)	−0.35 ± 0.75 (p = 0.02)	0.52 ± 1.40 (p < 0.05)
ΔHbA1c	0.40 ± 0.97 (p = 0.67)	0.28 ± 0.53 (p = 0.28)	−0.29 ± 1.20 (p = 0.02)

Data are presented as mean ± standard deviation or percentage. ACEI — angiotensin converting enzyme inhibitor; CABG — coronary artery by-pass graft; CHD — chronic heart disease; HbA1c — glycated hemoglobin; NSTEMI — non-ST-segment elevation myocardial infarction; PTCA — percutaneous transluminal coronary angioplasty; STEMI — ST-segment elevation myocardial infarction

Table 2. Cardiopulmonary test values pre- and post- cardiac rehabilitation (CR).

	Euglycemic (< 5.6) (n = 63)	IGT (5.6–7.0) (n=66)	Diabetics (> 7.0) (n = 19)	P
Watt pre-CR	128.5 ± 41.2	128.4 ± 40.0	104.7 ± 38.2	**0.02**
Watt post-CR	137.4 ± 44.0	142.1 ± 46.1	116.1 ± 41.3	0.08
METs pre-CR	5.7 ± 1.4	5.9 ± 1.9	4.8 ± 0.8	**0.03**
METs post-CR	6.6 ± 1.8	6.3 ± 1.8	4.9 ± 1.4	**0.01**
VO2-peak pre-CR	19.3 ± 5.3	20.1 ± 6.3	16.9 ± 3.8	0.07
VO2-peak post-CR	22.5 ± 5.9	21.5 ± 7.0	18.0 ± 4.4	**< 0.05**
VO2 threshold pre-CR	13.9 ± 4.2	14.7 ± 4.3	12.3 ± 2.5	0.11
VO2 threshold post-CR	16.0 ± 4.6	16.3 ± 4.6	13.7 ± 3.9	0.05
O2 beat pre-CR	12.3 ± 3.1	13.0 ± 3.5	11.6 ± 2.3	0.35
O2 beat post-CR	13.1 ± 3.4	13.5 ± 3.7	11.9 ± 2.9	0.19
Breathe reserve pre-CR	40.8 ± 15.9	38.1 ± 15.3	37.0 ± 13.5	0.33
Breath reserve post-CR	37.9 ± 17.1	37.0 ± 14.9	33.4 ± 14.6	0.31

Data are presented as mean ± standard deviation. Statistical significance is shown for euglycemic patients vs. diabetics. IGT — impaired glucose tolerance; METs — metabolic equivalents; VO2 — oxygen volume

Figure 1. Peak workload and VO2-peak improvement; **A.** Peak workload comparison between euglycemic (blue bars), impaired glucose tolerance (IGT; yellow bars) and diabetic patients (grey bars); **B.** VO2-peak comparison between euglycemic (blue bars), IGT (yellow bars) and diabetic patients (gray bars).

Figure 2. Linear regression, showing an inverse correlation between fasting glucose and VO2-peak improvement, suggesting that response to cardiac rehabilitation (CR) may be impaired by poor glycemic control.

Panel A

Watt

Panel B

ml/min/kg

Regression Equation:
deltapeak_vo2 = 6.419925 − 0.721243*glucose