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Predictors of Changes in Peak Oxygen Uptake After Outpatient Cardiac Rehabilitation: Importance of Cardiac Rehabilitation Attendance

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Abstract

Objective: To determine whether the number of cardiac rehabilitation (CR) sessions attended and selected clinical characteristics were predictive of patients who exhibited improvement in peak oxygen uptake (VO_2peak) after CR.

Patients and Methods: Using the Rochester Epidemiology Project records-linkage system, we identified all consecutive patients aged 18 years or older from Olmsted County, Minnesota, who underwent cardiopulmonary exercise testing before and after CR from 1999 to 2017. Regression models were created to assess the clinical predictors of VO_2peak improvement (>0% baseline) after CR.

Results: The analysis included 671 patients, of which 524 (78%) patients exhibited VO_2peak improvement after CR. The significant univariate predictors of VO_2peak improvement included younger age (odds ratio [OR], 0.98; 95% CI, 0.96-0.99), lower pre-CR VO_2peak (OR, 0.96; 95% CI, 0.94-0.99), and no history of peripheral artery disease (OR, 0.50; 95% CI, 0.31-0.81) (all, $P<.005$). The significant independent predictors of VO_2peak improvement from the multivariable analysis included the number of CR sessions (OR, 1.04; 95% CI, 1.02-1.05), younger age (OR, 0.96; 95% CI, 0.94-0.98), lower pre-CR VO_2peak (OR, 0.92; 95% CI, 0.89-0.95), and no history of peripheral artery disease (OR, 0.47; 95% CI, 0.28-0.78) (all, $P<.005$).

Conclusion: These findings highlight the importance of patient participation in CR sessions and individual clinical characteristics in influencing VO_2peak improvement after CR in patients with cardiovascular disease.

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Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] Cardiac rehabilitation (CR), a class 1 recommended therapy for secondary prevention, comprises an interdisciplinary chronic disease management program that has been shown to improve CVD risk factor management, quality of life, and medication adherence and provide group support and counseling.[2-7] Importantly, CR participation is associated with reductions in hospital readmissions and mortality in these patients.[8-11]

A crucial component of CR is the prescribed exercise training to elicit improvements in aerobic exercise capacity (ie, peak oxygen uptake [VO_2peak]). However, previous studies have found that an improvement in VO_2peak is not found in all patients after CR.[12-16] This is important as increasing VO_2peak after CR is associated with improved survival in these patients.[14,17] Recent studies have identified clinical factors including younger age, lower pre-CR VO_2peak, lower body mass index (BMI, calculated as the weight in kilograms divided by the height in meters squared), and male sex as common predictors of improving VO_2peak after CR.[13,14,18,19] A recent study has found that

VO_2peak was not improved after 16 CR sessions and proposed that a greater number of CR sessions are necessary to elicit VO_2peak improvements.[16] In contrast, other studies have found no differences in the number of CR sessions between patients who did and did not improve VO_2peak after CR.[12-14] As such, the impact of the number of CR sessions attended on VO_2peak improvement is unclear. As only approximately 57% and 27% of patients complete greater than 25 and 36 sessions of CR, respectively,[20] the identification of CR attendance as a predictor of improving VO_2peak has important clinical implications. Therefore, in this study, we investigated whether CR attendance and selected clinical factors were predictive of patients who exhibited improvements in VO_2peak after CR (ie, VO_2peak responder group).

PATIENTS AND METHODS

Study Design

This historical cohort study included consecutive patients who were referred and enrolled in an early outpatient (phase II) CR between June 1999 and July 2017 at Mayo Clinic, Rochester, Minnesota. All patients were residents of Olmsted County, aged 18 years and older, and had a cardiac event or procedure that was a clinical indication for CR. We included all patients during this timeframe who (1) completed cardiopulmonary exercise tests (CPETs) before and after CR participation (within 12 months), and (2) achieved a peak respiratory exchange ratio of more than or equal to 1 during both CPETs.[21] During this study period, there were 1264 sets of pre- and post-CR exercise stress tests, of which 874 consisted of CPETs (for both pre- and post-CR testing). Seventy sets of these CPETs were duplicates (ie, patient was enrolled in multiple CR programs during this period); therefore, there were 804 unique patients with pre- and post-CPETs associated with CR. Of these 804 patients, 133 were excluded for not meeting the respiratory exchange ratio criteria. As a result, 671 patients were considered in this analysis. This study was approved by Mayo Clinic Institutional Review Board. Per the Minnesota statute, only patients who had provided authorization to use their medical records for medical research were included.

Patient Identification

Clinical and sociodemographic characteristics were ascertained electronically using the Rochester Epidemiology Project, which is a record linkage system that captures clinical data (eg, diagnoses and vital signs) of all Olmsted County residents.[22-24] Clinical diagnoses were collected electronically using the *International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision* codes. At least 2 occurrences of a code (the same code or 2 different codes within the code set for a given disease) separated by more than 30 days and occurring within a 5-year capture frame before the index date were required for the diagnosis of a given comorbid condition. A random sample of these variables was reviewed in duplicate by 2 physician investigators for validation (A.C.S and J.M.I). Interobserver agreement for sociodemographic and clinical characteristics was excellent (all $\kappa > 0.85$). This research approach has been previously detailed and validated elsewhere.[25-27] Peripheral artery disease (PAD) included symptomatic and asymptomatic PAD. Similarly, diabetes diagnosis included type 1 and 2 diabetes in the present study.

Cardiac Rehabilitation

The comprehensive outpatient CR program at Mayo Clinic is based on the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines.[28] The patients were prescribed 36 supervised sessions that generally occurred over 3 days per week over 12-18 weeks. All patients attended at least 1 documented CR exercise session. Exercise prescriptions were individualized and updated as the patients progressed through the program. Patients participated in 30-45 minutes of supervised aerobic activity and an additional 10-15 minutes of strength training. The primary method for prescribing intensity during aerobic exercise was the Borg 6-20 rating of perceived exertion scale (with ratings of 12-14 ["somewhat hard"] for moderate-intensity training). In addition to CR exercise sessions, patients were encouraged to complete at least 30 minutes of moderate physical activity at home on days without supervised CR sessions. Additional education including healthy

TABLE 1. Patient Characteristics[a,b]

Variable	VO_2peak responders	VO_2peak nonresponders	Total	*P* value
N	524	147	671	
Age (y), mean ± SD	60±12	63±12	61±12	.005
Body mass index (kg/m^2), mean ± SD	29.5±5.3	29.3±5.6	29.5±5.3	.582
Female, n (%)	124 (24)	34 (23)	158 (24)	.893
Comorbidity				
Hypertension, n (%)	406 (78)	119 (81)	525 (78)	.367
Dyslipidemia, n (%)	474 (91)	133 (91)	607 (91)	.995
Chronic kidney disease, n (%)	156 (30)	47 (32)	203 (30)	.608
Chronic obstructive pulmonary disease, n (%)	213 (41)	62 (42)	275 (41)	.739
Diabetes, n (%)	311 (59)	89 (61)	400 (60)	.795
Peripheral artery disease, n (%)	59 (11)	30 (20)	89 (13)	.004
Current smoker or smoking history, n (%)	323 (62)	103 (70)	426 (64)	.061
Medication				
Antilipemic, n (%)	415 (79)	117 (80)	532 (79)	.917
Antiplatelet, n (%)	373 (71)	100 (68)	473 (71)	.458
Anticoagulant, n (%)	96 (18)	31 (21)	127 (19)	.449
ACEI/ARB, n (%)	276 (53)	83 (57)	359 (54)	.416
Beta-blocker, n (%)	404 (77)	111 (76)	515 (77)	.687
Calcium channel blockers, n (%)	124 (24)	45 (31)	169 (25)	.086
Diuretics, n (%)	222 (42)	65 (44)	287 (43)	.689
Cardiac rehabilitation				
CR sessions, mean ± SD	25.8±10.3	24.1±11.3	25.4±10.5	.182
Surgical indication, n (%)	136 (26)	38 (26)	174 (26)	.970

[a]ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CR, cardiac rehabilitation; VO_2, oxygen uptake.
[b]Surgical CR indication includes coronary artery bypass surgery, heart valve operation, and cardiac (or cardiac-lung) transplant.

nutrition, stress management, medication management and adherence, cardiovascular risk factor control, and proper sleep hygiene was delivered to CR patients.

Cardiopulmonary Exercise Testing

Data from the CPET were obtained electronically from an institutional registry. Patients completed a symptom-limited CPET before and after their CR program with the tests performed closest to CR enrollment and discharge used for analysis. All CPETs were performed by a clinical exercise physiologist or nurse, with cardiologist oversight. Patients completed an institutionally designed incremental exercise protocol on a motor-driven treadmill or cycle.[29-33] This protocol consisted of increasing 2 metabolic equivalents every 2 minutes with an end point of volitional fatigue. Cardiac medications were not withheld before CPET. Heart rate and rhythm were monitored continuously with a 12-lead electrocardiogram, and blood pressure was measured during each stage by manual sphygmomanometry. Ratings of perceived exertion were recorded for each stage and at peak exercise. Gas exchange variables were measured during exercise by indirect calorimetry (MGC Diagnostics). Measured variables included oxygen consumption, carbon dioxide production, and respiratory exchange ratio. Peak values were obtained by averaging the past 30 seconds of the test. O_2 pulse was determined by dividing oxygen consumption by heart rate.

Statistical Analyses

All analyses were completed using SAS statistical software (SAS Institute Inc.). Pre-CR patient characteristics are reported as mean ± SD for continuous variables and as n (%)

TABLE 2. Peak Cardiopulmonary Exercise Data[a,b]

	VO_2peak responders		VO_2peak nonresponders	
Variable	Pre-CR	Post-CR	Pre-CR	Post-CR
Test time (min)	7.3±2.2	8.6±2.3[c]	7.7±2.1	7.8±2.1[d]
RER	1.19±0.10	1.19±0.09	1.18±0.09	1.20±0.11
Heart rate (beats/min)	126±23	134±21[c]	128±22	119±24[c,d]
Heart rate (% predicted)	96±22	103±21[c]	96±19	91±20[c,d]
Systolic blood pressure (mm Hg)	151±37	163±29[c]	161±31	158±29[d]
Diastolic blood pressure (mm Hg)	65±16	65±16	67±18	66±17
O_2 pulse (mL/beat)	13.6±4.4	15.0±4.5[c]	14.5±3.9	13.9±4.0[c,d]
O_2 saturation (%)	97±4	97±3	97±3	98±2
RPE (Borg: 6-20)	18.2±0.9	18.4±0.7[c]	18.3±0.8	18.4±0.8

[a]CR, cardiac rehabilitation; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; VO_2, oxygen uptake.
[b]Data are presented as mean ± SD.
[c]Significantly different compared with pre-CR.
[d]Significant difference in the change from pre- to post-CR between groups.

for categorical variables. The pre- and post-CR variables were analyzed within and between the VO_2peak responder and nonresponder groups. The change from pre- to post-CR for each outcome was compared between groups using analysis of covariance models with the covariate of the pre-CR value included as a covariate in the model. Paired *t* tests were used to analyze variables from before to after CR within each group. VO_2peak improvement (ie, VO_2peak responder group) was defined as a VO_2peak percent increase of more than 0% from before to after CR. Associations between the number of CR sessions (as well as selected patient characteristics) and VO_2peak improvement were assessed with univariate logistic regression. Age, sex, and number of CR sessions, along with any significant factors in the univariate analysis, were added as covariates to the multiple logistic regression model. Odds ratios and their 95% CIs are reported. Statistical significance was defined as a P value of $<.05$.

RESULTS

In the study cohort, 671 patients were included, with a mean age of 61±12 years and BMI of 29.5±5.3 kg/m^2 (Table 1). The study cohort included 147 (22%) and 524 (78%) patients in the VO_2peak nonresponder and responder groups, respectively. The VO_2peak responder group was younger and less likely to have a history of PAD compared with the VO_2peak nonresponder group. No significant differences between the groups were found in other comorbidities, medications, or number of CR sessions (all, $P>.060$). Further, no differences were present in the number of days from pre-CR CPET to CR initiation (VO_2peak responder: 46±94 days vs VO_2peak nonresponder: 51±87 days) or CR completion to post-CR CPET (VO_2peak responder: 14±78 days vs VO_2peak nonresponder: 11±75 days) between groups (both $P>.101$).

In the whole cohort, the mean VO_2peak was 20.1±6.8 mL/kg per minute and 22.7±7.2 mL/kg per minute before and after CR, respectively, representing approximately 17% improvement for the group as a whole. The VO_2peak responder group exhibited a mean VO_2peak of 19.7±6.9 mL/kg per minute and 23.6±7.2 mL/kg per minute from pre- to post-CR, respectively, which represents an improvement of approximately 20%. The VO_2peak nonresponder group exhibited a mean VO_2peak of 21.5±6.1 mL/kg per minute and 19.5±6.3 mL/kg per minute from pre- to post-CR, respectively, which represents a decline of approximately 9%. Test time, peak exercise heart rate, systolic blood pressure, O_2 pulse, and ratings of perceived exertion increased from pre- to post-CR in the VO_2peak responder group (all $P<.001$; Table 2). The peak exercise heart rate and O_2 pulse were lower from pre- to post-CR in

TABLE 3. Predictors of VO_2peak Improvement Following CR[a,b]

Variable	Univariate			Multivariable		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (per 1 year)	0.98	0.96-0.99	.006	0.96	0.96-0.98	<.001
Female	1.03	0.67-1.59	.884	0.68	0.42-1.10	.119
CR sessions (per 1 CR session)	1.02	1.00-1.03	.086	1.04	1.02-1.05	<.001
Body mass index (per 1 kg/m^2)	1.01	0.97-1.04	.642	0.98	0.98-1.02	.283
Peripheral artery disease	0.50	0.31-0.81	.005	0.47	0.28-0.78	.004
Pre-CR relative VO_2 (per 1 mL/kg per min)	0.96	0.94-0.99	.004	0.92	0.89-0.95	<.001
Smoking history	0.68	0.46-1.02	.060			
History of hypertension	0.81	0.51-1.28	.363			
History of chronic obstructive pulmonary disease	0.94	0.65-1.35	.721			
History of diabetes	0.95	0.65-1.38	.782			
History of hyperlipidemia	1.00	0.53-1.86	.989			
Surgical CR indication	1.01	0.66-1.53	.970			
Days from pre-CR CPET to CR initiation	1.00	1.00-1.00	.629			
Days from CR completion to post-CR CPET	1.00	1.00-1.00	.677			

[a]CR, cardiac rehabilitation; VO_2, oxygen uptake.
[b]Surgical CR indication includes coronary artery bypass surgery, heart valve operation, and cardiac (or cardiac-lung) transplant.

the VO_2peak nonresponder group (all *P*<.001). Significant differences between the changes in test time and peak exercise heart rate, systolic blood pressure, and O_2 pulse from pre- to post-CR were present between the VO_2peak responder and nonresponder groups (all *P*<.001).

Significant univariate predictors of VO_2peak improvement following CR (ie, VO_2peak responder group) included younger age, lower pre-CR VO_2peak, and no history of PAD (Table 3) (all, *P*<.006). Sex, number of CR sessions, BMI; surgical vs nonsurgical indication, and history of smoking, hypertension, chronic obstructive pulmonary disease, diabetes, and dyslipidemia were not significant predictors of VO_2peak improvement following CR (all, *P*>.060). Multivariable analysis identified younger age, number of CR sessions, lower pre-CR VO_2peak, and no history of PAD as significant independent predictors of VO_2peak improvement after CR (Table 3) (all, *P*<.005).

DISCUSSION

The primary purpose of the present study was to identify readily available clinical predictors of VO_2peak improvement after CR. In our multivariable model, we found that independent predictors of VO_2peak improvement in patients who attended CR included a higher number of CR sessions, younger age, lower pre-CR VO_2peak, and no history of PAD. Our findings highlight the significant contribution of greater CR participation and other individual clinical characteristics in predicting the patients likely to exhibit VO_2peak improvement after CR.

In the present study, VO_2peak increased by 17% with CR participation in the whole cohort. However, 22% of the patients did not exhibit an improvement in VO_2peak after CR, whereas the VO_2peak responders had a 25% increase in VO_2peak after CR. The mean improvement in VO_2peak with CR herein is consistent with the previous studies that report an increase of 13%-35%.[12,13,17,18] However, previous studies have found heterogeneity in the change in VO_2peak, with VO_2peak not improving in some patients after CR.[12-16] To this point, these studies have found that VO_2peak does not improve in 14%-23% of patients after CR, which is consistent with the findings reported herein.[12-14,19] It should be noted that variable increases in VO_2peak after exercise training have also been reported in healthy older adults with multiple factors likely contributing (eg, genetics, exercise training program duration, etc.).[26,34-36] Nevertheless, this finding is clinically important considering greater VO_2peak improvement after CR is associated with better long-term survival.[14,17]

Although numerous studies have reported a variable change in VO_2peak after CR, minimal data identifying clinical factors associated with improving VO_2peak after CR in patients with CVD are available.[13,14,18,19] The primary purpose of the present study was to determine the impact of CR attendance on VO_2peak improvement after CR. Surprisingly, CR attendance was not different between the VO_2peak responder and nonresponder groups. However, in multivariable analysis adjusting for age, sex, BMI, PAD, and pre-CR VO_2peak, higher number of CR sessions was identified as an independent predictor of VO_2peak improvement after CR. Specifically, each CR session was associated with a 4% increase in the likelihood of improving VO_2peak. These findings are clinically relevant as previous studies have found that a 1% increase in VO_2peak is associated with a 2% decrease in cardiovascular mortality.[17] Further, an improvement in VO_2peak of 1 mL/kg per minute (66% of the patients achieved this in the present study) is associated with a 10% reduction in all-cause mortality.[14] Despite these beneficial effects of CR attendance on VO_2peak and mortality, CR attendance is low in the United States with numerous patient, hospital care/provider, and social-/environment-level factors playing a role.[7,37] The explanation for the discrepancy in CR attendance on VO_2peak improvement between the VO_2peak responder and nonresponder group comparison and multivariable analysis is unclear. However, as multiple clinical factors contribute to VO_2peak improvement (eg, age, pre-CR VO_2peak), this may suggest that adjusting for these established clinical variables that are associated with VO_2peak improvement are necessary to determine whether additional, novel clinical factors contribute to VO_2peak improvement after CR.

Additional independent predictors of VO_2peak improvement after CR included no history of PAD, a lower pre-CR VO_2peak, and older age. A novel finding of the present study was that PAD was associated with less of an improvement in VO_2peak after CR. These findings are in line with those of a previous study from HF-ACTION reporting that patients with heart failure with PAD exhibited blunted improvements in VO_2peak after exercise training compared with patients with heart failure without PAD.[38] These findings are clinically relevant as exercise capacity is a robust predictor of mortality in patients with PAD.[39] In addition, patients with PAD referred to CR are less likely to enroll and complete CR.[40] There is the potential that an extended CR duration is necessary to increase VO_2peak to allow these patients with PAD more pain-free exercise time.[41] In the present study, patients with the lowest VO_2peak before CR exhibited greater likelihood of increasing VO_2peak after CR. This finding is consistent with those of previous studies investigating CR as well as other therapeutic interventions on VO_2peak in patients with CVD.[13,14,18,30,33] Finally, younger age has also been reported to be a predictor of improving VO_2peak after CR in line with the present study.[14,18] Taken together, these findings suggest that the development of innovative CR program strategies is critical to maximize CR attendance and optimize individualized treatments for patients with PAD to facilitate VO_2peak improvement after CR.

The present study has several methodological considerations that should be considered when interpreting the findings. First, this study is a retrospective, single-center study; thus, causation cannot be implied. Second, selection bias may have occurred as only patients with pre- and post-CR CPETs were included by design. Third, our cohort primarily included men. Finally, physical activity performed outside CR and the intensity of exercise performed during each CR session were not recorded and, therefore, not included in the present analysis. To this latter point, higher exercise intensity has previously been reported to be a predictor of VO_2peak improvement after CR.[13,18,19] Nonetheless, these factors may affect the generalizability, but not the interval validity, of our work. Future studies are necessary to determine how to optimize the number of CR sessions and exercise intensity during CR to maximize VO_2peak improvement in patients with CVD.

In conclusion, in this large cohort study, we found that the number of CR sessions attended and no history of PAD were the key predictors of VO_2peak improvement after CR in patients with established CVD. These findings demonstrate the importance of CR participation and individual clinical characteristics (eg, PAD) in influencing VO_2peak improvement after CR in patients with CVD.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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Author Little and Dr Smith contributed equally to this work.

Abbreviations and Acronyms: **BMI,** body mass index; **CPET,** cardiopulmonary exercise test; **CR,** cardiac rehabilitation; **CVD,** cardiovascular disease; **PAD,** peripheral artery disease; **VO_2peak,** peak oxygen uptake

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