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 (VO₂peak) 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 VO₂peak improvement (>0% baseline) after CR.

Results: The analysis included 671 patients, of which 524 (78%) patients exhibited VO₂peak improvement after CR. The significant univariate predictors of VO₂peak improvement included younger age (odds ratio [OR], 0.98; 95% CI, 0.96-0.99), lower pre-CR VO₂peak (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 VO₂peak 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 VO₂peak (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 VO₂peak improvement after CR in patients with cardiovascular disease.

Cardiovascular disease (CVD) is the leading cause of death in the United States. 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. Importantly, CR participation is associated with reductions in hospital readmissions and mortality in these patients.

A crucial component of CR is the prescribed exercise training to elicit improvements in aerobic exercise capacity (i.e., peak oxygen uptake [VO₂peak]). However, previous studies have found that an improvement in VO₂peak is not found in all patients after CR. This is important as increasing VO₂peak after CR is associated with improved survival in these patients. Recent studies have identified clinical factors including younger age, lower pre-CR VO₂peak, 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 VO₂peak after CR. A recent study has found that...
VO₂peak was not improved after 16 CR sessions and proposed that a greater number of CR sessions are necessary to elicit VO₂peak improvements. In contrast, other studies have found no differences in the number of CR sessions between patients who did and did not improve VO₂peak after CR. As such, the impact of the number of CR sessions attended on VO₂peak improvement is unclear. As only approximately 57% and 27% of patients complete greater than 25 and 36 sessions of CR, respectively, the identification of CR attendance as a predictor of improving VO₂peak 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 VO₂peak after CR (ie, VO₂peak 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. 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-CR 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. 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. 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. 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...
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. O₂ 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 (%)
for categorical variables. The pre- and post-CR variables were analyzed within and between the VO2peak 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 co-variate in the model. Paired t tests were used to analyze variables from before to after CR within each group. VO2peak improvement (ie, VO2peak responder group) was defined as a VO2peak 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 VO2peak 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/m² (Table 1). The study cohort included 147 (22%) and 524 (78%) patients in the VO2peak nonresponder and responder groups, respectively. The VO2peak responder group was younger and less likely to have a history of PAD compared with the VO2peak 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 (VO2peak responder: 46±94 days vs VO2peak nonresponder: 51±87 days) or CR completion to post-CR CPET (VO2peak responder: 14±78 days vs VO2peak nonresponder: 11±75 days) between groups (both P > .101).

In the whole cohort, the mean VO2peak 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 VO2peak responder group exhibited a mean VO2peak 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 VO2peak nonresponder group exhibited a mean VO2peak 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, O2 pulse, and ratings of perceived exertion increased from pre- to post-CR in the VO2peak responder group (all P < .001; Table 2). The peak exercise heart rate and O2 pulse were lower from pre- to post-CR in

| Variable                          | VO2peak responders Pre-CR | Post-CR | VO2peak nonresponders Pre-CR | Post-CR |
|-----------------------------------|---------------------------|---------|-----------------------------|---------|
| Test time (min)                   | 7.3±2.2                   | 8.6±2.3 | 7.7±2.1                     | 7.8±2.1 |
| 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 | 128±22                      | 119±24 |
| Heart rate (% predicted)         | 96±22                     | 103±21 | 96±19                       | 91±20 |
| Systolic blood pressure (mm Hg)  | 151±37                    | 163±29 | 161±31                      | 158±29 |
| Diastolic blood pressure (mm Hg) | 65±16                     | 65±16 | 67±18                       | 66±17 |
| O2 pulse (mL/beat)               | 13.6±4.4                  | 15.0±4.5 | 14.5±3.9                   | 13.9±4.0 |
| O2 saturation (%)                | 97±4                      | 97±3 | 97±3                        | 98±2   |
| RPE (Borg: 6-20)                 | 18.2±0.9                  | 18.4±0.7 | 18.3±0.8                   | 18.4±0.8 |

aCR, cardiac rehabilitation; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; VO2, oxygen uptake.
bData are presented as mean ± SD.
cSignificantly different compared with pre-CR.
dSignificant difference in the change from pre- to post-CR between groups.
the VO2peak nonresponder group (all P < .001). Significant differences between the changes in test time and peak exercise heart rate, systolic blood pressure, and O2 pulse from pre- to post-CR were present between the VO2peak responder and nonresponder groups (all P < .001).

Significant univariate predictors of VO2peak improvement following CR (i.e., VO2peak responder group) included younger age, lower pre-CR VO2peak, and no history of PAD (all P < .001). Significant univariate predictors of VO2peak improvement following CR (i.e., VO2peak responder group) included younger age, lower pre-CR VO2peak, and no history of PAD (all P < .001).

In the present study, VO2peak increased by 17% with CR participation in the whole cohort. However, 22% of the patients did not exhibit an improvement in VO2peak after CR, whereas the VO2peak responders had a 25% increase in VO2peak after CR. The mean improvement in VO2peak here-in is consistent with the previous studies that report an increase of 13%-35%.

To this point, these studies have found heterogeneity in the change in VO2peak, with VO2peak not improving in some patients after CR. However, previous studies have found heterogeneity in the change in VO2peak, with VO2peak not improving in some patients after CR. 12-16

DISCUSSION
The primary purpose of the present study was to identify readily available clinical predictors of VO2peak improvement after CR. In our multivariable model, we found that independent predictors of VO2peak improvement in patients who attended CR included a higher number of CR sessions, younger age, lower pre-CR VO2peak, 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 VO2peak improvement after CR.
of improving VO2peak. These findings are clinically relevant as previous studies have found that a 1% increase in VO2peak is associated with a 4% increase in the likelihood of improving VO2peak 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 VO2peak improvement after CR. Specifically, each CR session was associated with a 4% increase in the likelihood of improving VO2peak. These findings are clinically relevant as previous studies have found that a 1% increase in VO2peak is associated with a 2% decrease in cardiovascular mortality.17 Further, an improvement in VO2peak 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 VO2peak and mortality, CR attendance is low in the United States with numerous patient, hospital care/provider, and social/environment-level factors playing a role.7,57 The explanation for the discrepancy in CR attendance on VO2peak improvement between the VO2peak responder and nonresponder group comparison and multivariable analysis is unclear. However, as multiple clinical factors contribute to VO2peak improvement (eg, age, pre-CR VO2peak), this may suggest that adjusting for these established clinical variables that are associated with VO2peak improvement are necessary to determine whether additional, novel clinical factors contribute to VO2peak improvement after CR.

Additional independent predictors of VO2peak improvement after CR included no history of PAD, a lower pre-CR VO2peak, and older age. A novel finding of the present study was that PAD was associated with less of an improvement in VO2peak 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 VO2peak 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 VO2peak to allow these patients with PAD more pain-free exercise time.41 In the present study, patients with the lowest VO2peak before CR exhibited greater likelihood of increasing VO2peak after CR. This finding is consistent with those of previous studies investigating CR as well as other therapeutic interventions on VO2peak in patients with CVD.13,14,18,30,33 Finally, younger age has also been reported to be a predictor of improving VO2peak 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 VO2peak 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 VO2peak 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 VO2peak 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 VO₂peak improvement after CR in patients with established CVD. These findings demonstrate the importance of CR participation and individual clinical characteristics (eg, PAD) in influencing VO₂peak improvement after CR in patients with CVD.

POSSIBLE COMPETING INTERESTS
The authors report no competing interests.

ACKNOWLEDGMENTS
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; VO₂peak, peak oxygen uptake

Grant Support: The work was supported by the National Institutes of Health (NR-018832 [T.P.O.], T32 HL071111 [J.R.S, and S.M.H.], and K12 HD056987 [J.R.S.]). This publication was also made possible through the support of the Mary Kathryn and Michael B. Panitch Career Development Award in Hypertension Research Honoring Gary Schwartz, MD (J.R.S.).

Publication dates: Received for publication June 17, 2022; accepted for publication July 15, 2022.

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