Review Article

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심장재활치료에 반응하지 않는 환자

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Non-responders to Cardiac Rehabilitation

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Abstract

Despite being treated with cardiac rehabilitation (CR) programs, some patients do not improve on outcome measures, including peak oxygen consumption. These are called cardiac rehabilitation non-responders, and research is ongoing to determine how to define them, how their prognosis differs from responders, what causes them, and how to treat them. Attempts have been made to explain non-responsiveness through differences in baseline cardiorespiratory fitness, program adherence, and anthropometric measures including body composition and body mass index prior to starting cardiac rehabilitation. While some groups advocate aggressive treatment and intervention for non-responders, citing high mortality and readmission rates, others are attempting to identify variables that may better reflect reality, suggesting that the commonly used variables have limited clinical significance. These include peak oxygen consumption, which might be merely a numbers game since there is no discernible difference in these prognostic indicators and functional levels after a certain period for those who perform above a certain threshold. Hopefully, researchers involved in cardiac rehabilitation will conduct clinical research and laboratory studies with the non-responders discussed in this narrative review in mind. This will enable them to uncover unknown aspects and assist in improving treatment for these individuals.

Key Words

Cardiac rehabilitation, Non-responders, Prognosis, Responsiveness

Introduction

Multidisciplinary programs in CR, which include exercise training, are beneficial enough to be recommended by guidelines for patients with cardiovascular disease. The importance of CR for patients with heart disease, including ischemic heart disease (IHD) and heart failure (HF), is widely recognized, and efforts are already

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underway to promote and facilitate it. However, they are underutilized, with significant gaps in referral, access, and participation. Furthermore, there are questions regarding which patients would benefit from these programs and how best to implement them [1]. Furthermore, even if medical professionals provide an appropriate CR program, the degree of improvement after treatment can vary depending on factors such as age, sex, comorbidity, CR attendance [2-4]. In addition, there are "non-responders" who do not respond to treatment at all, rather than only showing a difference in the degree of improvement after treatment. There is no consensus on the definition of these non-responders, and many different studies have defined varying definitions, resulting in differing views on their clinical utility. Although this narrative review does not provide a clear-cut definition of non-responders, I hope that by understanding the concept of non-responders, you will be able to consider their clinical significance in clinical practice and research. This understanding may aid you in identifying their causes and developing appropriate intervention strategies.

Main Text

1) Classification by patient group–HF, IHD, and cardiac surgery

The degree of improvement may vary, but aerobic exercise or resistance exercise increases exercise capacity in patients with heart failure, which is one of the main goals of cardiac rehabilitation therapy. However, some patients do not show improvement as expected and remain as non-responders.

In a study exploring the characteristics of non-responders in a CR program for congestive heart failure, it was found that heart rate (HR) recovery and peak HR at 1 minute were significant predictors of a positive training response. Conversely, characteristics observed in non-responders, such as HR reserve less than 30 beats per minute (bpm), HR recovery less than 6 bpm, and peak HR less than 101 bpm, were identified as factors distinguishing between groups. This suggests impaired chronotropic capacity as a potential cause of non-response. [5]. The researchers of this study define responders as follows: someone who achieved at least one of the following improvements: (1) an increase in peak VO_2 by ≥ 5%; (2) an increase in workload by ≥ 10%; and (3) a decrease in VE/VCO_2 slope by ≥ 5% [5].

One study identified non-responders to exercise training in patients with coronary artery disease. They defined non-responders as those with a gain in VO_2peak (ΔVO_2peak) of < 1 ml/kg/min over 12 weeks of aerobic interval training or aerobic continuous training. Approximately 14% were non-responders, and characteristics such as higher baseline peak oxygen uptake and oxygen uptake efficiency slope, history of elective percutaneous coronary intervention, older age, lower training intensity and lower baseline physical activity were associated with non-responders [6].

In other study for 93 patients aged 65 years and older who underwent all cardiac surgeries except minimally invasive procedures like transcatheter aortic valve implantation, responsiveness was assessed using the Short Physical Performance Battery (SPPB) [7]. They defined responsiveness as follows: individuals whose SPPB score improved by 2 points or more from the start of prehabilitation and exceeded 11 points were classified as the responder group. Those whose SPPB score did not exceed 11 points immediately before surgery were classified as non-responders. Prehabilitation period was 5.4 ± 4.1 days. The non-responder group had significantly lower score of balance, gait, rise and total SPPB score after prehabilitation and score of balance, rise, and total SPPB at postoperative day 5 compared to the responder group. The responder group experienced quicker enhancements in postoperative physical function and achieved ambulatory independence sooner compared to the non-responder group. Conversely, the non-responder group had a lower preoperative skeletal muscle index, more severe preoperative New York Heart Association (NYHA) classification, and a history of musculoskeletal disease or

stroke.

Another study on patients undergoing septal myectomy for hypertrophic cardiomyopathy defines non-responders as those with a change in VO_2peak of less than 0% from pre- to post-myectomy [3]. This study showed that demographic factors (e.g., female sex), lack of enrollment in cardiac rehabilitation, and cardiovascular risk factors (e.g., history of dyslipidemia) predict which patients did not experience increases in VO_2peak after septal myectomy surgery.

2) Influential factor

(1) CR attendance

The outcomes of individuals who did not participate well in prehabilitation before procedures or surgeries, or in the cardiac rehabilitation program afterward, are expected to be naturally unfavorable, as confirmed in several studies. [3,4,7]. Multivariable analysis of 671 patients who underwent CR regardless of disease type, defining responders as those with a VO_2peak percent increase of more than 0% from baseline, revealed an odds ratio (OR) for the number of CR sessions (OR = 1.04; 95% CI 1.02-1.05, $p < 0.001$) [4]. Lack of CR enrollment was a independent predictor for non-responders (OR = 0.56; 95% CI, 0.35-0.96, $p < 0.03$).

(2) Age

Younger age (OR = 0.96; 95% CI, 0.94-0.98) was independent predictors for responders group after CR program [4]. The idea that younger age is a favorable (responders) predictor and older age is an unfavorable (non-responders) predictor ultimately expresses the same concept, older age was also an independent predictor of VO_2peak non-responders in myomectomy (OR = 1.03; 95% CI, 1.01-1.06, $p < 0.001$) [3], and in coronary artery disease (OR = 1.11; 95% CI, 1.04-1.18, $p = 0.001$) [6].

(3) Sex

Regarding sex, there was no clear direction observed, and in each study, women appeared as an independent predictor of non-responders (OR = 2.01; 95% CI,1.87-2.97, $p < 0.001$) [3], or showed no significance [4].

(4) VO_2

While reviewing the results to write this narrative review, one of the most interesting findings pertained to VO_2peak. Although the study populations were somewhat different-comprising all patients in CR regardless of etiology versus patients in CR specifically for coronary artery disease-the results were completely opposite regarding baseline VO_2peak before starting CR. In the study for patients in CR regardless of etiology, lower pre-CR VO_2peak (OR, 0.92; 95% CI, 0.89-0.95) independent predictors of VO_2peak improvement after CR [4].

By the contrast, higher baseline VO_2peak (OR = 1.16, 95% CI, 1.06-1.27, $p = 0.001$) were independent predictors of exercise non-response in coronary artery disease patients [6]. In a between-group comparison, exercise non-responders were older, their baseline peak oxygen uptake and oxygen uptake efficiency slope were higher than responders [6].

Furthermore, higher pre-myectomy VO_2peak (OR = 1.06 95% CI, 1.04-1.08 $p < 0.001$) was a predictor for non-responders in patients undergoing septal myomectomy for hypertrophic cardiomyopathy [3]. As will be described later, this underscores the need for additional research, such as studies meticulously adjusting for diseases or conditions to be considered, or large-scale cohorts employing propensity matching.

(5) Comorbidity and other conditions

Independent predictors of VO_2peak improvement after CR are no history of peripheral artery disease (OR, 0.47; 95% CI, 0.28-0.78) [4]. The OR for non-responders was higher in cases with a history of elective percutaneous coronary intervention (OR = 3.31, 95% CI, 1.12-9.76, $p = 0.030$) [6], dyslipidemia (OR = 1.62; 95% CI, 1.22-2.42, $p < 0.04$) [3]. But, dyslipidemia was not predictors in other study [4]. Diabetes mellitus (DM) did not emerge as a significant independent predictor in patients who

underwent myomectomy or received CR [3], regardless of the underlying cause [4].

Therefore, the identical disease can exhibit different outcomes, posing challenges for interpretation. One potential solution regarding comorbidity that has been considered is the following study [8]. A comorbidity score was calculated based on the presence and severity of conditions such as peripheral vascular disease, cerebrovascular disease, chronic lung disease, or orthopedic limitations. Each condition was assigned a severity score: 1 for present but not exercise-limiting, 2 for impacting exercise performance, and 3 for exercise-limiting. The total comorbidity score ranged from 0 to 12. The comorbidity score in this study demonstrated an r value of - 0.20, R2 value of 0.04, and p value < 0.0001, correlating with the percentage change in peak oxygen uptake.

In myomectomy patients, a low body mass index was an independent predictor of non-responders BMI (OR = 0.96, 95% CI, 0.93-0.99, p = 0.03) [3], but it did not show significance in patients with all-cause etiology (OR = 0.98, 95% CI, 0.98-1.02, p = 0.283) [4]. NYHA classification did not show significance [3] in myomectomy patients.

3) Clinical considerations

In non-responders, a clinically significant difference that can be observed is primarily related to mortality rate. Although limited to specific cases of septal myectomy in patients with hypertrophic cardiomyopathy, the mortality rate of the VO_2peak non-responder group was approximately 77% higher after adjustment for age, sex, beta-blocker use, coronary artery disease history, and body mass index compared with the VO_2peak responder group (adjusted hazard ratio: 1.77, 95% confidence interval: 1.06-3.34, p = 0.01).

In many different types of studies, age and gender are recognized as significant factors influencing outcomes. To the CR non-responders, firstly, it can be intuitively anticipated that older age may lead to a higher likelihood of being a non-responder. Secondly, although we cannot predict the direction of the gender effect, we anticipate differences in outcomes, with non-responders seemingly more prevalent among females upon review. However, further research or clarification of the results is needed for patients with different conditions to ensure consistent application of factors such as baseline VO_2peak and comorbidities. Because various factors that may not intuitively seem connected are related to non-responders, it is crucial to thoroughly assess these factors and apply a personalized and tailored treatment program optimized for each individual.

Additionally, consideration should be given to utilizing wearable heart rate variability monitoring and other methods in cardiac rehabilitation programs to reduce CR non-responders [9-12].

Conclusion

Developing a consensus on the definition of cardiac rehabilitation non-responders and identifying their causes and appropriate intervention strategies are as vital as promoting cardiac rehabilitation itself.

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