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Interleukin-6 Reduction as a Predictor of Functional Capacity Improvement after Phase II Cardiac Rehabilitation Programme in Coronary Artery Bypass Surgery Patients

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ABSTRACT

Introduction: Improved functional capacity is a good prognostic value in patients after CABG. Phase II cardiac rehabilitation provides beneficial effects on physical function, cardiopulmonary function, inflammatory response, autonomic function, and improves functional capacity, and there is a significant decrease in Interleukin-6 values in patients after CABG. Several studies have selected Interleukin 6 as an inflammatory cytokine that can be used to assess the beneficial effects of cardiac rehabilitation in coronary heart disease conditions. The aim of the study was to determine the relationship of Interleukin-6 value as a predictor of functional capacity improvement after phase II cardiac rehabilitation in patients undergoing CABG.

Method: This study was analytic observational study conducted retrospectively on 31 CABG patients who underwent phase II cardiac rehabilitation. Data collection on functional capacity, Interleukin-6 examination before and after phase II cardiac rehabilitation. Data were analyzed univariately and bivariately to assess the relationship between Interleukin-6 and functional capacity. Multivariate analysis will then be performed using linear regression. The relationship test will be performed with Pearson correlation test. Statistical data analysis using SPSS software, p value <0.05 is statistically significant.

Results: There were 29 samples. The results of the cardiac exercise test showed an increase in distance at the end of phase II cardiac rehabilitation compared to the initial examination (457,655 ± 24,346 vs 180,482 ± 13,941). At the end of the examination there was a decrease in the average Interleukin-6 level from 24.412 ± 2.516 to 13.647 ± 1.413. There was a significant relationship between improvement in functional capacity and Interleukin-6 (p=0.032, r=0.40). An increase of 1 MET will decrease Interleukin-6 by 2.238 pg/mL. There was a decrease in mean Interleukin-6 from 24,412±2,516 to 13,647±1,413 at the end of phase II with p value <0.001.

Conclusion: Interleukin-6 can be a predictor of improved cardiac functional capacity after phase II cardiac rehabilitation program in patients undergoing BPAK.

Keywords

Interleukin-6, functional capacity, Coronary artery disease, CABG

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INTRODUCTION

The prevalence of cardiovascular disease based on data from the National Health and Nutrition Examination Survey (NHANES) in 2013-2016 is 48% and continues to increase with age. This rate is the leading cause of death for cardiovascular disorders in the United States.[1,2] From the World Health Organization (WHO) 2016 data, it is estimated that 17.9 million people died due to cardiovascular disease (44% of all deaths due to non-communicable diseases), 7.4 million of which were caused by coronary heart disease, followed by stroke with 6.7 million people.[1]

Coronary heart disease occurs when the coronary arteries that supply the myocardium harden and narrow. This occurs due to an inflammatory process and the build-up of cholesterol in the walls of the coronary arteries, referred to as atherosclerosis. The ongoing process of atherosclerosis will cause the lumen of the coronary blood vessels to narrow, resulting in obstructed blood flow. Heart muscle that is deprived of oxygen supply due to decreased blood flow causes symptoms such as chest pain or heart attack.[3]

Atherosclerosis is a chronic inflammatory process whose course is triggered by traditional risk factors such as hypercholesterolemia, causing changes in the blood vessel wall. The progression of atherosclerosis will continue as long as the inflammatory process occurs to cause cardiovascular events.[4] Inflammation is an essential process in atherogenesis, and many inflammatory markers have been analysed for their association with long- and short-term prognosis in patients with coronary heart disease.[5] Chen and Jerome reported that inflammation has a key role in atherosclerosis. Interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) are two pro-inflammatory cytokines that are important in the acute inflammatory phase. IL-6 is secreted in response to Interleukin 1-β (IL-1β) and Tumour Necrosis Factor-α (TNF-α) and hs-CRP release from the liver by IL-6 secretion.[6]

Improvements in functional capacity can be achieved after aerobic exercise. Functional capacity will increase by 33% after aerobic exercise and maximal oxygen uptake (VO2Max) will increase by 16%.[7] Any increase of 1 METs of functional capacity is known to reduce 12% of mortality risk in patients with heart disease.[8] The effects of cardiac rehabilitation are known to be associated with inflammatory markers including fibrinogen, TNF-α,16,17 and IL-6.[9] Several studies have selected high-sensitivity Interleukin-6 (IL-6) levels as an inflammatory marker that can be widely used to assess the beneficial effects of cardiac rehabilitation on inflammatory states. Chen et al. investigated that Yoga training can reduce inflammatory cytokines, LDL, cholesterol levels in healthy women.[6]

The efficacy of cardiac rehabilitation with mind-body exercises in yoga with inflammatory biomarkers has been studied in recent years. Exercise is a core component of cardiac rehabilitation programmes and its anti-inflammatory effects help explain how physical activity reduces cardiovascular disease (CVD) and mortality. Research by Cesari et al. showed that cardiac rehabilitation has positive effects on health and metabolic factors including inflammatory markers among CVD patients.

METHOD

Study Design

This study is a retrospective study to assess the role of Interleukin-6 as a predictor of improvement in functional capacity after phase II cardiac rehabilitation in patients undergoing coronary artery bypass surgery at H. Adam Malik Hospital Medan. The study was conducted at Hajj Adam Malik Hospital Medan starting in July 2022 and continued until the sample size was met.

Population and Sample

The target population was patients diagnosed with CHD who underwent coronary artery bypass surgery. The target population was patients diagnosed with CHD who underwent BPAK and phase II cardiac rehabilitation at Haji Adam Malik Hospital starting from July 2022 until the sample size was met. The sample is an affordable population that meets the inclusion and exclusion criteria. Sampling was done by consecutive sampling method. Researchers only observe and record data contained in patients.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were subjects with CHD after BPAK surgery who underwent phase II cardiac rehabilitation at Haji Adam Malik Hospital Medan. Patients with Type 5 IMA, patients with worsening symptoms of heart failure decompensation, patients with impaired liver function, patients with renal impairment, patients with malignancy, and patients with infection were included as exclusion criteria.

Procedure

Research subjects with a diagnosis of CHD who have undergone BPAK surgery are carried out phase I cardiac rehabilitation. When they were allowed to go home for outpatient treatment, the subjects were re-educated to undergo phase II of the cardiac rehabilitation programme. Then the purpose of the study was explained and the subject was asked to sign an informed consent. After that, various necessary parameters were measured including: Interleukin-6 levels, BMI, and 6MWT. Then the patient was given an exercise prescription to be done independently at home.

After that, the patient began undergoing a phase II cardiac rehabilitation programme at HAM Hospital which was carried out in the gym room for 3 sessions per week for 4 weeks. The types of exercises undertaken were aerobic exercises such as leisurely walking, running on a treadmill, and pedalling a stationary bicycle. Each session was preceded by warm-up movements and ended with a cool-down. Before and after the phase II cardiac rehabilitation procedure, the patient's vital signs such as blood pressure, pulse and breathing frequency were measured. The duration of each session is at least 30 minutes and the type of exercise is adjusted to the patient's ability. In addition to exercise activities, patients also undergo counselling once per week, which includes discussing the progress the patient feels during the rehabilitation process, difficulties experienced by the patient, recommendations regarding diet and lifestyle, and motivation to increase adherence to the program. During the phase II cardiac rehabilitation programme, all patient examination and treatment data are recorded in full.

Upon completion of the phase II cardiac rehabilitation programme, patients were recommended to undergo a cardiac exercise test for programme evaluation. Various necessary parameters such as Interleukin-6, BMI and 6MWT were measured. The patient was then educated on the activities allowed, the types of exercise recommended, and the prescription of exercises for home. After that, data was processed using SPSS.

Data Management and Analysis

Statistical data processing and analysis used the SPSS programme. Data were compared by independent T-test or Mann Whitney U-test, while categorical data were compared by Chi-square test. Variables with a p value <0.05 were included for multivariate analysis.

Research Ethics

This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, University of North Sumatra and a research permit from Litbang Haji Adam Malik Medan.

RESULT

Research Characteristics

This study was conducted at the Department of Cardiology and Vascular Medicine of the Integrated Heart Centre of the H. Adam Malik Hospital, Medan, by sampling a total of 31 CHD patients who had undergone the BPAK procedure and undergone phase II cardiac rehabilitation. 2 samples were excluded in this study (1 person died and 1 person loss to follow up).

Table 1. Basic Characteristics of Study Subjects

Variable	N (%)
Age	54,172 ±1,471
Type sex	
Man	26 (89.7)
Woman	3 (10.2)
BPAK method	
On Pump	21 (72.4)
Off Pump	8 (27.6)
Cardiomegaly	
Yes	18 (62.1)
No	11 (37.9)

Table 2. Pre-test and Post-test Results of Cardiac Rehabilitation

Variable	Rehabilitation Heart Phase I	Rehabilitation Heart Phase II	p value
BMI	26.4207 ±0.675	25,889 ±0.583	0.233
6 Minute walk test	180,482 ±13,941	457,655 ±24,346	<0.001
IL-6	24,412 ±2,516	13,647 ±1,413	<0.001
Capacity Functional	3.109 ±0.250	8,093 ±0.444	<0.001

The results of subject characteristics before and after cardiac rehabilitation are presented in table 4.2. In the examination conducted during phase I cardiac rehabilitation, the average BMI in this study was 26,4207±0.675 kg/m2. This value decreased at the end of phase II cardiac rehabilitation to 25,889±0,583 kg/m2. Based on the results of the cardiac exercise test, there was an increase in distance at the end of phase II cardiac rehabilitation compared to the beginning of the examination (457,655±24,346 vs 180,482±13,941).

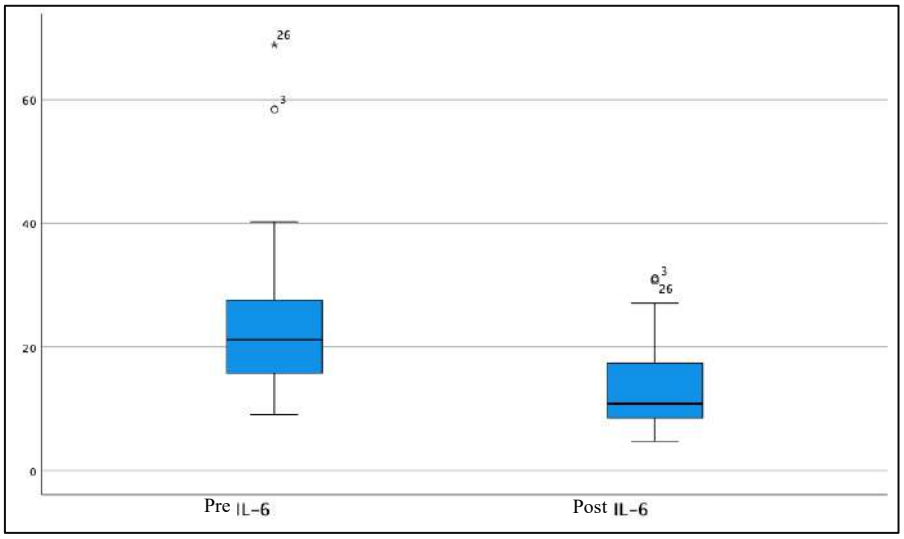

Fig 1. Decrease in IL-6 values after phase II rehabilitation

Fig. 1 shows the changes in IL-6 values in cardiac rehabilitation phase I and phase II. There was a decrease in mean IL-6 from 24,412±2,516 to 13,647±1,413 at the end of phase II with a p value <0.001. Fig. 2 illustrates the changes in the mean functional capacity of the heart in cardiac rehabilitation phase I and phase II. There was a significant increase in the mean functional capacity from 3,109±0,250 in phase I cardiac rehabilitation to 8,093±0,444 at the end of phase II with a p value of <0.001.

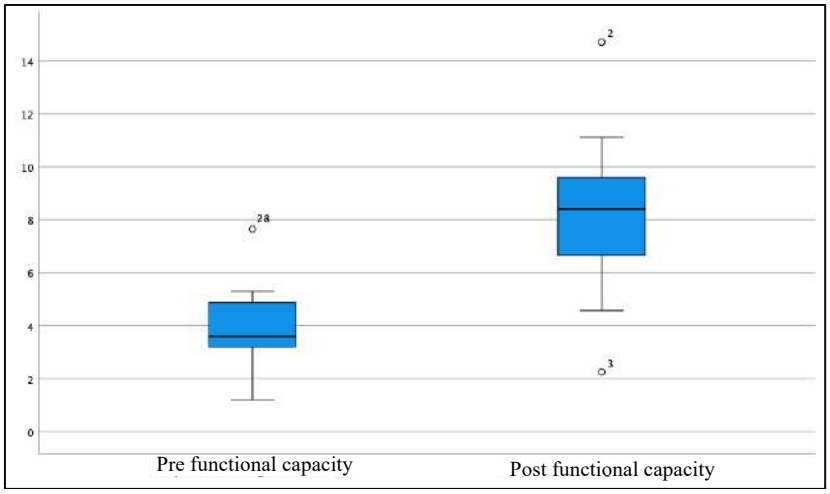

Fig. 2 Improvement in cardiac functional capacity after phase II rehabilitation

Correlation of Baseline Characteristics, Echocardiography and Inflammatory Biomarkers with Improved Cardiac Functional Capacity and Decreased IL-6

The results of bivariate analysis are presented in table 4.3. Age has a significant relationship to the improvement of functional capacity with moderate correlation strength (p=0.012, r=-0.460), but there is no significant relationship between age and IL-6 reduction. Gender had a significant relationship with changes in cardiac functional capacity and IL-6 reduction in this study. In this study, there was no relationship between the BPAK method and the improvement of cardiac functional capacity and IL-6 reduction.

IL-6 value at the beginning of the examination showed a significant correlation with moderate correlation ability to the improvement of cardiac functional capacity (p=0.032, r=-0.400). IL-6 value at the beginning of the examination also influenced the decrease in IL-6 value at the end of phase II (p=0.009, r=0.478). The functional capacity value before phase II cardiac rehabilitation also had a significant correlation with the increase in functional capacity at the end of phase II (p=0.008). The correlation value obtained was 0.483, indicating that there was a positive correlation between functional capacity before phase II cardiac rehabilitation and functional capacity improvement with moderate correlation ability. Initial functional capacity also had a correlation with the decrease in IL-6 at the end of phase II (p=0.005, r=-0.508).

Table 3. Bivariate Analysis of Correlation of Baseline Characteristics, Echocardiography, and Inflammatory Biomarkers with Improved Cardiac Functional Capacity and Decreased IL-6

Variable	Change Capacity Functional	IL-6 changes
Age	P=0.012 r=-0.460	P=0.932 r=0.016
Type sex	P=0.031 r=0.510	P=0.023 r=0.402
BPAK method	P=0.460 r=0.143	P=0.548 r=0.245
Cardiomegaly	P=0.004 r=0.523	P=0.084 r=0.260
Early IL-6	P=0.032 r=-0.400	P=0.009 r=0.478
Initial 6MWT	P=0.155 r=0.271	P=0.025 r=0.416
Capacity Function beginning	P=0.008 r=0.483	P=0.005 r=-0.508

The results of the analysis of functional capacity improvement on IL-6 changes are presented in table 4. There was a significant relationship between improvement in functional capacity and IL-6 with good correlation strength. Every 1 MET increase will decrease IL-6 by 2.238 pg/mL.

Table 4. Correlation Analysis of Functional Capacity Improvement with IL-6 Changes

Variable	β	p value	IK95% (Min- max)		r
Change capacity functional	-2,238	0,000	-3.123	-1,263	-0.666

Multivariate Analysis of Risk Factors for Improvement in Cardiac Functional Capacity

Multivariate analysis used to determine which factors are predictors of improved cardiac function capacity in patients undergoing BPAK is presented in table 4.5. In the analysis, IL-6 and initial functional capacity value before phase II cardiac rehabilitation were statistically significant predictors.

Table 5. Multivariate analysis of risk factors for improvement in cardiac functional capacity

Variable	β	p value	IK95% (Min- max)	
Age	-0.96	0.60	-0.197	0.004
Early IL6	-0.066	0.017	-0.120	-0.013
Capacity function beginning	0.612	0.050	-0.001	1,226
Constant	12,557			

DISCUSSION

This study showed that at the end of cardiac rehabilitation there was an increase in average functional capacity from 3,109±0,250 METs in phase I cardiac rehabilitation to 8,093±0,444 METs at the end of phase II with a p value <0.001. These results are in line with previous studies, which found a significant increase in cardiac functional capacity in all subjects after the cardiac rehabilitation programme. The study by Shabani also

showed an increase in functional capacity in post BPAK patients with an initial functional capacity of 7,72±1,6 to 10,72±1,30 after the cardiac rehabilitation programme (p<0.001).[10]

An increase in 1 MET in patients with and without cardiovascular risk factors showed a 28-51% reduction in the risk of fatal cardiac death and a 17-29% reduction in the risk of non-fatal cardiac death. A decrease in 1 MET is a strong prognostic factor for cardiac death.[11] This increase in functional capacity is believed to be more closely related to the peripheral effects than the central effects of the heart on cardiac rehabilitation. Peripheral muscles utilise oxygen from aerobic exercise more effectively by increasing the number and size of enzymes associated with aerobic and mitochondrial processes, as well as increasing the amount of myoglobin and capillary blood vessels in the muscle. Improved functional capacity in patients with coronary heart disease can prevent physical disability and also prevent recurrence of coronary heart disease and death.[12]

In this study, there was a decrease in mean IL-6 from 24,412±2,516 to 13,647±1,413 at the end of the rehabilitation phase (p<0.001). This result is supported by previous research, IL-6 levels have decreased significantly from 26±2,3 before cardiac rehabilitation to 13,3±2,6 after cardiac rehabilitation (p<0,001).[13] The study of Vijayaraghava et al. considered the role of Yoga on pro-inflammatory markers. Their study showed that regular Yoga training reduced IL-6 and TNF-α levels after endurance and strength training.[14] The results of another study also mentioned that there was a decrease in IL-6, CRP and TNF-α after aerobic exercise and resistance training. These findings differ from the study by Fathollahi where although there was a decrease in IL-6 after a cardiac rehabilitation programme from 10.90 to 8.77, there was no significant association between cardiac rehabilitation and IL-6 reduction.[15]

These results suggest that exercise can influence systemic inflammatory markers. Three mechanisms that may explain the anti-inflammatory effects of exercise are decreased visceral fat mass, decreased numbers of pro-inflammatory monocytes in the circulation, and increased circulating T cells. Cardiorespiratory fitness is also associated with a decrease in low-grade inflammation which may be caused by an increase in the ability of immune cells to suppress inflammatory responses through adrenergic receptors.[16]

Based on the results of this study, there was a correlation between the initial value of the inflammatory marker IL-6 and the improvement in functional capacity after phase II cardiac rehabilitation (p=0.032; r=-0.400). Every 1 MET increase will decrease IL-6 by 2.238 pg/mL. Previous research showed a significant negative correlation between IL-6 and muscle mass in the elderly population (P=0.032; r=-0.577).[17] In individuals with stable coronary artery disease, higher IL-6 was associated with worse prognosis in 6 years of follow-up. A 1 pg/mL increase in IL-6 was associated with a 1.7 times increased risk of myocardial infarction or sudden death.[18]

In multivariate analysis, baseline IL-6 before phase II rehabilitation was a statistically significant predictor factor. Previous studies have shown different functional capacity improvement effects depending on inflammatory markers that describe pro-inflammatory and pro-fibrotic processes after a 12-week cardiac rehabilitation programme. Low inflammatory marker values in patients with heart failure tended to have better peak VO2 improvement. This suggests that inflammation may cause different responses to the rehabilitation programme and may explain the reduced functional capacity. This could be due to inflammation directly inhibiting the effects of exercise. IL-6 can affect oxygen uptake in muscle through transduction by transmembrane receptor unit glycoprotein 130. IL-6 can also cause endothelial dysfunction, decreased mitochondrial activity and skeletal muscle apoptosis. These effects will inhibit the increase in peak VO2 with exercise.[19]

CONCLUSION

Interleukin-6 can be a predictor of improved cardiac functional capacity after phase II cardiac rehabilitation program in patients undergoing BPAK.

DECLARATIONS
The research has received approval from Universitas Sumatera Utara and Adam Malik Hospital Health Research and Ethics Committee. All participants were informed about subject of the study.

CONSENT FOR PUBLICATION
The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS
The authors declare that there is no conflict of interest in this research.

AUTHORS' CONTRIBUTIONS
All authors are responsible for conceptualization, manuscript preparation, manuscript editing, and manuscript assurance.

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