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Inflammatory Mediators as Predictors of Improved Functional Capacity after Phase 2 Cardiac Rehabilitation in Coronary Artery Bypass Surgery Patients

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ABSTRACT

Background: Inflammatory parameters correlate with the atherosclerotic acute coronary syndrome (ACS) process and can predict future cardiovascular events in healthy populations. Coronary heart disease (CHD) subjects who had undergone coronary artery bypass grafting (CABG) procedures and underwent cardiac rehabilitation must be prevented from increased cardiovascular events. The study aims to evaluate the effect of cardiac rehabilitation programs on marker inflammation of cardiovascular risk factors.

Method: This study was conducted at Departement Cardiology and Vascular Diseases Integrated Heart Center H. Adam Malik Hospital Medan who had undergone CABG procedures and underwent phase I and II cardiac rehabilitation. All subjects were carried out to collect basic patient data based on anamnesis, physical examination, results of laboratory tests, and functional capacity of the heart.

Result: The subjects of this study were male 26 (89.7%) subjects and female 3 (10.2%) subjects. The average BMI in this study was 26.4207±0.675 kg/m2, the most common CHD risk factor was smoking in 21 (72.4%) subjects, dyslipidemia in 20 (69%) subjects, hypertension in 18 (62.1%) subjects, obesity 14 (48.3%) subjects and T2DM 13 (44.8%) subjects. Based on echocardiography results, the average ejection fraction was 47.931±2.17 %, and 18 (62.1%) subjects had cardiomegaly. After undergoing phase I and II cardiac rehabilitation, there was improved significantly of the 6-minute walk test to hsCRP, IL-6, neutrophil-lymphocyte ratio (NLR), and functional capacity (all, p <0.001). IL-6 value is

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correlated significantly with functional capacity improvement ($p<0.05$) in both phase I and II cardiac rehabilitation.

Conclusion: Cardiac rehabilitation (CR) should be considered as a preventive plan in the treatment of CHD patients. Physical exercise is noteworthy and they reduce morbidity and mortality due to reduced inflammation.

Keywords: Cardiac Rehabilitation, Coronary Artery Disease, IL-6, hsCRP, Capacity Functional of heart.

ABSTRAK

Latar Belakang: *Parameter inflamasi berkorelasi dengan proses sindrom koroner akut aterosklerotik (ACS) dan dapat memprediksi kejadian kardiovaskular di masa depan pada populasi sehat. Subjek penyakit jantung koroner (PJK) yang telah menjalani prosedur pencangkokan bypass arteri koroner (CABG) dan menjalani rehabilitasi jantung harus dicegah dari peningkatan kejadian kardiovaskular. Penelitian ini bertujuan untuk mengevaluasi pengaruh program rehabilitasi jantung terhadap marker inflamasi faktor risiko kardiovaskular.*

Metode: *Penelitian ini dilakukan di Departement Cardiology and Vascular Diseases Integrated Heart Center H. Adam Malik Hospital Medan yang telah menjalani prosedur CABG dan menjalani rehabilitasi jantung fase I dan II. Semua subjek dilakukan untuk mengumpulkan data dasar pasien berdasarkan anamnesis, pemeriksaan fisik, hasil tes laboratorium, dan kapasitas fungsional jantung.*

Hasil: *Subjek penelitian ini adalah laki-laki 26 (89,7%) subjek dan perempuan 3 (10,2%) subjek. Rata-rata IMT dalam penelitian ini adalah 26,4207±0,675 kg/m2, faktor risiko PJK yang paling umum adalah merokok pada 21 (72,4%) subjek, dislipidemia pada 20 (69%) subjek, hipertensi pada 18 (62,1%) subjek, obesitas 14 (48,3%) subjek dan T2DM 13 (44,8%) subjek. Berdasarkan hasil ekokardiografi, rata-rata fraksi ejeksi adalah 47,931±2,17%, dan 18 (62,1%) subjek mengalami kardiomegali. Setelah menjalani rehabilitasi jantung fase I dan II, terjadi peningkatan signifikan pada tes jalan kaki 6 menit terhadap hsCRP, IL-6, NLR, dan kapasitas fungsional (semua, p <0,001). Nilai IL-6 berkorelasi signifikan dengan peningkatan kapasitas fungsional (p<0,05) pada rehabilitasi jantung fase I dan II.*

Kesimpulan*: Rehabilitasi jantung harus dipertimbangkan sebagai rencana pencegahan dalam pengobatan pasien PJK. Latihan fisik patut diperhatikan dan mereka mengurangi morbiditas dan mortalitas karena berkurangnya peradangan.*

Kata kunci*: Rehabilitasi Jantung, Penyakit Arteri Koroner, IL-6, hs-CRP, Kapasitas Fungsional jantung.*

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1 Introduction

Coronary Heart Disease (CHD) is the single most common cause of death and its frequency is increasing Worldwide. CHD now accounts for nearly 1.8 million annual deaths, or 20% of all deaths in Europe, although with large variations between countries. Acute coronary syndrome (ACS) occurs 3-4 times more frequently in men than women under the age of 60 years, but after the age of 75 years, women represent the majority of patients.[1] Inflammatory parameters correlate with the atherosclerotic process and can predict future cardiovascular events in healthy populations. Inflammation parameters are also used as indicators of successful treatment and secondary prevention.[2]

Cardiac rehabilitation (CR) should be considered as a preventive plan in the treatment of CHD patients. Although the benefits of CR programs based on physical exercise are noteworthy and they reduce morbidity and mortality due to CAD phenomena, these courses are almost expensive, time-consuming, and ineffective in some cases.[3] Exercise capacity is related to several factors including age, foreleg strength during knee extension, muscle mass, hemoglobin (Hb), brain natriuretic peptide (BNP), C-reactive protein (CRP), and kidney function.[4]

The blood biomarker pentraxin-3 is increased in acute coronary syndrome. Pentraxin-3 measured during early stages was found to be a prognostic marker in patients with AMI. Plasma pentraxin-3 levels are elevated in patients with vasculitis, acute myocardial infarction, inflammation or systemic sepsis, psoriasis, unstable angina pectoris, and heart failure. [1] Regarding this aspect, physical exercise is beneficial in patients with cardiac dysfunction, especially in patients with pre-pentraxin-3 levels between 0.40 and 0.55 ng/dL and not in patients with pre-pentraxin-3 levels less than 0.40 ng/dL. These findings suggest a potential predictive role for PTX3 in inferring CR outcomes in patients after CABG.[3] The study aims to evaluate the effect of cardiac rehabilitation programs on marker inflammation of post-CABG

2 Methods

This study is an observational research design using consecutive sampling methods at the Department of Cardiology and Vascular Diseases Integrated Heart Center H. Adam Malik Hospital Medan, and the study starting in March 2022 until the number of samples is fulfilled. Inclusion criteria were subjects with CHD undergoing phase 2 cardiac rehabilitation. Exclusion criteria were patients with IMA type 5, worsening symptoms of decompensated heart failure, liver dysfunction, kidney dysfunction, and malignancy.

2.1 Statistical Analysis

The data will be analyzed using the Statistical Package for Social Sciences (SPSS). Pearson product-moment correlation coefficient or Spearman's rank correlation coefficient was used to assess correlations among variables as appropriate. Multivariable linear regression models were performed considering the distance walked at 6-MWT at the beginning and at the end of CR and the relative Δ meters (which was also normalized for expected values) as the dependent variables,

respectively; independent predictors were selected including the most clinically important baseline variables characterized by statistical significance Pearson correlation coefficients (see methods section). The level of significance will be set at $\alpha = 5\%$.

3 Results

Of 29 CHD subjects who had undergone CABG procedures and underwent phase I cardiac rehabilitation were carried out to collect basic patient data based on anamnesis and physical examination, results of laboratory tests, and functional capacity of the heart. The age of the subjects is 54.172±1,471 years old.

Based on Table 1, The subjects of this study were dominated male sex, namely 26 people (89.7%) and 3 female subjects (10.2%). The most common CHD risk factor in this study was smoking in 21 (72.4%) subjects, dyslipidemia in 20 (69%) subjects, hypertension in 18 (62.1%) subjects, obesity in 14 (48.3%) subjects, and diabetes in 13 (44.8%) subjects. Based on echocardiography results, the average ejection fraction is 47.931±2.17. On chest X-ray examination, 18 subjects (62.1%) had cardiomegaly.

Table 1 Characteristics of Research Subject

Variable	N (%)
Gender	
Male	26 (89.7)
Female	3 (10.2)
Smoking	
Yes	21 (72.4)
No	8 (27.6)
Diabetes	
Yes	13 (44.8)
No	16 (55.2)
Hypertension	
Yes	18 (62.1)
No	11 (37.9)
Dyslipidemia	
Yes	20 (69)
No	9 (31)
Menopause	
Yes	3 (10.3)
No	26 (89.7)
Obesity	
Yes	14 (48.3)
No	15 (51.7)
BPAK method	
Pump on	21 (72.4)
Pump off	8 (27.6)
Cardiomegaly	
Yes	18 (62.1)
No	11 (37.9)

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Based on Table 2, the results of echocardiography, the average ejection fraction was 47.931±2.17, and 18 (62.1%) subjects had cardiomegaly. After undergoing phase I and II cardiac rehabilitation,

there was improvement significantly of the 6-minute walk test, hs-CRP, IL-6, NLR, and functional capacity (all, p <0.001)

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

Variable	Cardiac Rehabilitation Phase I	Cardiac Rehabilitation Phase II	P Value
IMT	26.4207± 0.675	25.889±0.583	0.233
6 Minute walk test	180.482±13.941	457.655±24.346	0.001*
hs-CRP	5.244±0.482	0.475±0.095	0.001*
IL-6	24.412±2.516	13.647±1.413	0.001*
NLR	4.279±0.459	2.266±0.191	0.001*
Functional capacity	3.109±0.250	8.093±0.444	0.001*

Based on Table 3, there is a correlation significantly between cardiovascular risk factors with functional capacity and IL-6 (*: p<0.05)

Table 3 The Correlation Between Cardiovascular Risk Factors and Cardiac Functional Capacity and IL-6

Variable	Changes in Functional Capacity		IL-6	
	r	p	r	p
Old	-0.460	0.012*	0.016	0.932
Gender	0.510	0.031*	0.402	0.023*
Smoking	-0.510	0.791	-0.113	0.913
Diabetes	0.190	0.325	0.24	0.238
Hypertension	0.207	0.207	0.301	0.529
Dyslipidemia	-0.153	0.427	-0.18	0.854
Menopause	0.402	0.031*	0.305	0.023*
Obesity	-0.101	0.603	-0.092	0.774
BPAK Method	0.143	0.460	0.245	0.548
Fraction Ejection	0.320	0.091	0.405	0.029*
Cardiomegaly	0.523	0.004*	0.260	0.084
Initial hsCRP	0.501	0.006*	0.314	0.098
Initial IL-6	-0.400	0.032*	-	-
Initial NLR	-0.037	0.848	0.114	0.557
Initial 6MWT	0.271	0.155	0.416	0.025*
Initial functional capacity	0.483	0.008*	-0.508	0.005*

* p < 0.05

Based on Table 4, The results of the analysis of increased functional capacity for changes in IL-6. There is a significant relationship between functional capacity improvement and IL-6 with good correlation strength. For every 1 MET increase, there will be a decrease in IL-6 of 2.238 mg/L.

Table 4 Correlation Analysis of Improved Functional Capacity Against Changes in IL-6

Variable	β	P value	95% CI (Mi-Max)		r
Changes in Functional Capacity	-2.238	0.000	-3.123	-1.263	-0.666

Based on Table 4, Multivariate analysis was used to determine which factors were predictors of increased functional capacity of the heart in patients undergoing BPAK presented in Table 5.

In the Multivariate analysis, there was a statistically significant of hs-CRP, IL-6, and initial functional capacity as predictors of functional capacity improvement (all, $p < 0.05$).

Table 5 Multivariate Analysis of Risk Factors on Functional Capacity Improvement

Variable	β	Nilai p	95% CI (Min-maks)	
Step 5				
Early hsCRP	0.361	0.014	0.079	0.642
Early IL6	-0.671	0.012	-0.118	-0.016
Initial functional capacity	0.618	0.033	0.505	1.181
Constant	5.452			

4 Discussion

CABG is still an important insult, associated with several potential acute-phase complications like stroke, transient neurocognitive impairment, dehiscence of sternotomy, mediastinitis, myocardial infarction, pericardial tamponade, pericarditis, hemo- or pneumothorax, pleural effusion, acute renal failure, lower limb edema, anemia, infection, and atrial fibrillation or flutter,[5]–[7] being much more aggressive then percutaneous transluminal coronary angioplasty, the most frequently used myocardial revascularization technique. Patient's after CABG are prescribed a complex drug regime and recommended to adopt a healthy lifestyle, including smoking cessation, diet, moderate exercise, and psychological stress control. Adherence to these behaviors is usually voluntarily adopted early after CABG but becomes more difficult in the long term.[8], [9]

Considering the patient's need to obtain a full and prompt physical recovery after surgery to allow a fast normalization of daily life activities (including the return to work), linked with the need to adopt a healthy lifestyle and the specific pharmacological regime for a lifetime, cardiac rehabilitation (CR), as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their efforts, preserve or resume optimal functioning in their community and through improved health behavior, slow or reverse progression of the disease.[10]

Exercise has beneficial effects that can mediate the improvement in functional capacities, such as endothelial function and regeneration,[11] but its effect on inflammation in patients with heart failure is still not well understood. In healthy individuals, it appears to exist an 'acute phase response' to exercise, where inflammatory biomarkers, particularly IL-6, increase in the blood soon after strenuous exercise and diminish after a few days.[12], [13] Regardless of its acute effects, some studies have suggested that 'chronic' exercise has anti-inflammatory effects because it reduces blood levels and muscular expression of IL-6, TNF-alpha, and other pro-inflammatory cytokines. Noteworthy, most participants in these studies were not taking beta-blockers.[14], [15] On the other hand, exercise did not significantly change the blood levels of these inflammatory biomarkers in our study, in which all patients were under optimized clinical treatment according to current guidelines.[16] Such divergent results may be related to different populations and

treatments for heart failure. Indeed, an analysis of the HF-ACTION study failed to demonstrate a significant reduction of the blood levels of high-sensitivity C-reactive protein after three months of exercise.[17]

This study shows that at the end of cardiac rehabilitation, there is an average increase in functional capacity from 3.109±0.250 MET to 8.093±0.444 MET at the end of phase II ($p<0.001$). These results are in line with research by Santos et al, in patients who underwent inspiratory muscle training (IMT) and resistance training showed a 22.5% increase in peak VO2.[18] Another study showed that there was an increase in peak VO2 postoperative CABG patients by 18.1 ± 15.2 from the initial value after a cardiac rehabilitation program.[19] The results of previous studies also showed a significant increase in the MET value of postoperative CABG patients after cardiac rehabilitation ($p\leq0.05$).[20]

This study also showed an increase in the 6 minutes walking test after the cardiac rehabilitation program, with an average of 6 MWT of 180.482±13.941 before the program and increased to 457.655±24.346 after the phase II cardiac rehabilitation program ($p<0.001$).

Research by Solak found an increase in 6MWT in post-CABG patients, from 389.1 ± 88.5 before the rehabilitation program to 495.0 ± 99.1 after the cardiac rehabilitation program ($p < 0.005$). According to Stahle, there is a 15% increase in 6-MWT distance in elderly patients with acute myocardial infarction after aerobic exercise intervention. Exercise can improve cardiovascular function by increasing oxygen distribution throughout the body through the process of vasodilation and angiogenesis. Exercise also increases the process of biogenesis in adipocytes, skeletal muscle cells, and cardiac muscle cells.[21]

In this study, a correlation was found between the initial value of the inflammatory marker IL-6 and hsCRP on the increase in functional capacity after phase II cardiac rehabilitation. These results are supported by the results of a previous study by Tiksnadi et al that initial hsCRP levels had a positive correlation with functional capacity improvement (0.004; 0.461). Patients with a higher initial 1mg/L hsCRP can affect the decrease in hsCRP after cardiac rehabilitation of 0.877 mg/L.[2] In this study, a significant negative correlation was found between IL-6 and functional capacity improvement. Previous studies have shown a significant negative correlation between IL-6 and muscle mass in the elderly population (0.032; -0.577).[22]

It is expected that, after the performance of the mobilization protocol, started earlier, the patients in the IG will have an improvement in the distance walked in the 6MWT, which will be assessed during 7 postoperative days and 60 days after hospital discharge, and will have less time in ICU and lower prevalence of pulmonary complications when compared to the CG. It is also expected that with the results obtained from this study, it will be possible to introduce an early mobilization protocol in the ICU routine unit and sensitize the medical board about the importance of proper physiotherapy conduct.[23]

5 Conclusion

Cardiac rehabilitation (CR) after CABG clearly shows a decrease in all-cause or cardiovascular mortality, although it may seem logical. The evidence supporting that CR was recommended for post-CABG is mainly based on the extrapolation for CABG patients of the evidence from CR programs after ACS.

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