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Original Article

Cardiac Rehabilitation and Change of Plasma Cardiac Biomarkers in Patients with Coronary Artery Disease: A Prospective Single-Center Study

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SUMMARY

Background: Cardiac rehabilitation (CR) has been proven to have benefits including reduced mortality, reduced cardiovascular events, and improved functional capacity. This study aimed to investigate the difference in the response of multiple biomarkers in patients with coronary artery disease (CAD) following CR therapy.
Methods: Biomarkers, including N-terminal-pro B-type natriuretic peptide (NTproBNP), midregional atrial natriuretic peptide (MRproANP), MR-pro adrenomedullin (MRproADM), C-reactive protein (CRP), and soluble suppressor of tumorigenicity (sST2) were sampled, and a cardiopulmonary exercise test was conducted at enrolment and after completion of the study. Physician-supervised exercise protocol consisted of a 6-month program with three sessions of physical training per week.
Results: This study included 23 patients (19 men, median age: 65 years). After the 6-month exercise protocol, there was a significant decrease in CRP levels (0.4 vs. 0.3 mg/L, p = 0.006) and NTproBNP levels (86.5 vs. 85.7 pg/mL, p = 0.017) before and after CR program. In contrast, there was a significant increase in MRproADM, MRproANP, and neopterin levels before and after CR (122.4 vs. 236.7 pg/mL, p = 0.005; 129.4 vs. 198.0 pg/mL, p < 0.001 and 6.6 vs. 10.2 nmol/L, p < 0.001, respectively).
Conclusions: Our findings suggest that a 6-month program of CR has benefits on cardiac function and is considered an important nonpharmacological strategy in patients with mild CAD.

1. Introduction

Cardiovascular (CV) disease is the leading cause of mortality in the world[1] and the second leading cause of mortality in Taiwan.[2] Reducing CV events beyond controlling traditional CV risk factors such as diabetes mellitus (DM), hypertension, and dyslipidemia is a critical issue. Cardiac rehabilitation (CR) reduces CV mortality and enhances cardiopulmonary function.[3] A meta-analysis showed that CR reduced CV mortality and re-hospitalization by approximately 20%.[4] Therefore, CR referral is recommended in the treatment guidelines for patients with stable coronary artery disease (CAD).[5,6] Previous studies have reported that exercise-based CR improves functional capacity; however, the individual response to exercise among CR patients is variable.[7] Therefore, individual differences in cardiac adaptation of patients receiving CR therapy should be understood; additionally, the optimal treatment regimen during CR should be considered. The molecular mechanisms underlying the effects of exercise have been investigated. Circulating biomarkers can provide information regarding the potential pathways of the body's physiologic responses to exercise. Moreover, the role of biomarkers as a guide to optimize CR therapy needs to be identified.

Biomarkers are detectable and measurable indicators and can help monitor organ functions or pathophysiological states in response to an intervention.[8] There are several commonly used biomarkers such as natriuretic peptides and C-reactive protein (CRP) and novel biomarkers that are associated with adverse CV events. Different biomarkers have been used as surrogate indicators of adverse CV events including myocardium stress, representing myocardial stretch (i.e., N-terminal pro brain natriuretic peptide [NTproBNP] and midregional pro atrial natriuretic peptide [MRproADP]); remodeling (i.e., soluble isoform of suppression of tumorigenicity 2 [sST2]); neurohumoral activation (i.e., midregional proadrenomedullin [MRproADM]); oxidative stress (i.e., neopterin); and inflammation (i.e., CRP). A higher sST2 level (≥ 26.8 ng/mL) is associated with a higher incidence rate of adverse CV events among stable CAD patients.[9] NTproBNP, growth-differentiation factor-15, MRproANP, cystatin C, and MRproADM were the strongest predictors of adverse CV outcomes in 1781 stable CAD patients with at least one stenosis of ≥ 30% present in a major coronary artery.[10] Higher neopterin (> 15 nmol/L) level was associated with a higher risk of adverse CV events in 123 stable CAD patients with stent implantation.[11]

Therefore, we selected various biomarkers to represent multiple pathways involved in CAD. This prospective study aimed to investigate the difference of potential biomarkers reflecting cardiac function and inflammation in patients with CAD before and after CR therapy.

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2. Methods

2.1. Study sample

This is a single-center prospective cohort observation study. Patients who was CAD (single vessel disease [SVD]) underwent coronary stent deployment within three years prior to entering the study were enrolled. Patients with acute coronary syndrome (ACS), acute myocarditis, decompensated heart failure, aortic aneurysm, severe aortic stenosis, pulmonary embolism, uncontrolled arrhythmia, heart failure (HF, New York Heart Association Functional Classification [NYHA] III–IV) and hemodialysis were excluded. Electronic medical records were reviewed to obtain information regarding the patients' demographic characteristics, medical history, biochemistry data, and drug history. The echocardiography of all subjects showed no regional wall motion abnormality. Hypertension was defined as (1) known history of hypertension; (2) taking anti-hypertensive drugs at referral; and (3) systolic blood pressure (BP) $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg. Patients were considered to have DM if they had a known history of diabetes (HbA1c $\geq$ 6.5%), fasting glucose higher than 126 mg/dL, or were taking glucose lowering agents. Every patient who provided written informed consent underwent a 6-month CR program. At baseline and after the 6-month CR program, all patients underwent a functional evaluation that included clinical evaluation, cardiopulmonary exercise test (CPET), and blood biomarker measurements. The study started in August 1, 2018 and ended in July 31, 2019. This study was approved by the Internal Review Board (IRB) of Mackay Memorial Hospital (IRB approval No. 17MMHIS175).

2.2. The exercise intervention

Rehabilitation specialists developed the exercise intervention. The exercise intervention targeted patients with CAD and consisted of a 6-month program with three sessions of physical training per week. Each session lasted for 40 minutes and was supervised by the physical therapist in the hospital. Before exercise training, a baseline CPET was performed to assess the functional capacity and maximal heart rate. The aerobic exercise program was divided into a 10-minute warm-up phase including stretching, range of motion, and low intensity exercises. The warm-up phase was followed by a 20-minute main aerobic exercise course targeting the heart rate with treadmill training; subsequently, a 10-minute cool-down phase was performed. The 20-minute aerobic exercise phase was subdivided into three incremental exercise steps, which varied in duration and intensity. The duration was shortest in the first and last exercise step (between 2 to 5 minutes) and longest in the second step (between 10 to 15 minutes). Exercise intensity was determined individually at 50–60% of the maximum heart rate obtained by previous CPET. The intensity was adjusted according to the individual's progress and tolerance in the following session. CPET was performed using a cycle ergometer with an individualized ramp protocol according to established guidelines. The ramp protocol consisted of 3 min of unloaded cycling, and then increasing 10 or 15 W/min until exhaustion. Expired gas was collected and continuously analyzed using the Cortex system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany). All patients were encouraged to achieve maximal effort by monitoring the respiratory exchange ratio at > 1.10. During the whole exercise session, the patient's heart rate and blood pressure were under ECG surveillance. The participants who smoke are required to quit smoking. Several parameters were obtained from CPET, including peak oxygen consumption (peak VO_2), oxygen pulse, workload and minute ventilation/carbon dioxide production (VE/VCO_2) slope. Peak VO_2 was calculated as the mean value of three measures of VO_2 during the final 30 seconds of test. O_2 pulse was determined by dividing peak oxygen consumption by heart rate. The VE/VCO_2 slope was determined using linear regression analysis of VE and VCO_2 obtained throughout the exercise period.

2.3. Measurements of biomarkers

The blood samples were drawn before entering the CR program and the day after the end of the last exercise test. For blood collection, the patients were instructed to fast overnight; blood was collected after the patient rested in the sitting position for at least 10 minutes. We performed serial measurements of six serum biomarkers including NTproBNP, MRproADM, MRproANP, neopterin, sST2, and CRP in every patient undergoing outpatient CR program. Whole blood was collected into EDTA-containing tubes and the plasma was stored at -20 °C. ELISA was performed to measure plasma levels of CRP (SEA821Hu, Cloud-clone corp, Houston, USA), sST2 (ARG81260, Arigo Biolaboratories Corporation, Hsinchu City, Taiwan), NTproBNP (DY3604, R&D Systems, Minneapolis, MN, USA), neopterin (MBS495060, Mybiosource Inc, San Diego, USA), MRproANP (MBS750904, Mybiosource Inc, San Diego, USA), and MRproADM (MBS2516133, Mybiosource Inc, San Diego, USA).

2.4. Statistical analysis

Continuous data, not following normal distribution, are presented as median (interquartile range [IQR]) and categorical data as percentage. The Wilcoxon matched-pairs test for pair values was used to compare variables before and after CR. The differences of biomarkers between before and after CR were evaluated using analysis of covariance (ANCOVA) with adjustment for variables before CR. SPSS software, version 22.0, was used for statistical analyses, and significance was assumed at $p < 0.05$.

3. Results

3.1. Patient characteristics

This study included 23 patients (19 men [82.6%], median age of 65 years). Participants in the study had a median duration of 20 months after stent deployment. The baseline characteristics of our study population are shown in Table 1. The percentages of beta-blocker, angiotensin converting enzyme inhibitor/angiotensin II receptor blockers, and statin use were 60.9%, 69.5% and 78.3%, respectively.

3.2. Laboratory parameters

Peak VO_2 levels were significantly higher after the end of CR program than those at baseline (22.3 ml/kg/minute [IQR: 20.0, 25.2] vs. 19.1 ml/kg/minute [IQR: 18.2, 22.3], $p < 0.001$). Oxygen pulse (Peak VO_2/HR) levels were significantly higher after the end of CR program than those at baseline (10.9 [IQR: 10.2, 13.3] vs. 10.6 [IQR: 9.7, 13.2], $p = 0.04$). CRP levels were significantly lower after the end of the CR program than those at baseline (0.3 mg/L [IQR: 0.1, 0.5] vs. 0.4 mg/L [IQR: 0.2, 0.7], $p = 0.006$). Additionally, NTproBNP levels were significantly lower after the end of the CR program than those at baseline (85.7 [IQR: 79.9, 95.4] vs. 86.5 pg/mL [IQR: 81.7, 106.4], $p = 0.017$). In contrast, MRproADM levels were significantly higher after the end of CR program than those at baseline (236.7 pg/mL

[IQR: 152.3, 300.7] vs. 122.4 pg/mL [IQR: 96.2, 167.1], p = 0.005). Similarly, MRproANP levels were significantly higher after the end of the CR program than at baseline (198.0 pg/mL [IQR: 156.5, 245.0] vs. 129.4 pg/mL [108.2, 163.9], p < 0.001). Additionally, neopterin levels were significantly higher after the end of the CR program than those at the baseline (10.2 nmol/L [IQR: 8.7, 14.6] vs. 6.6 [IQR: 5.0, 9.8], p < 0.001). However, no significant difference was noted between the levels of workload, VE/VCO_2 slope, sST2, low density lipoprotein cholesterol, and high density lipoprotein cholesterol before and after the CR program (Table 2).

The dynamic change for all parameters at baseline and 6 months after CR are shown in Figure 1. A linear model (ANCOVA), adjusting for parameters before CR, was used to estimate the CR effect on parameters after CR. There was a borderline significant interaction between MRproANP and NTproBNP after CR (p = 0.05). Our results found a significant interaction effect on the change in MRproANP and MRproADM levels after CR (p < 0.001).

4. Discussion

This study investigated the effect of CR on the changes of multiple plasma biomarkers in patients with CAD (SVD) and stent deployment. The findings showed that 1. CR significantly improved peak VO_2 in patients with mild CAD and 2. NTproBNP and CRP levels were significantly decreased, but MRproANP, MRproADM, and neopterin levels were increased after the CR program. The subjects with CAD and increased VO_2 (2.5 mL/kg/minute) after CR had lower mortality rate than those without lack of improvement by VO_2.[12] In FITR Heart Study, 12 months CR can improved peak VO_2 at high-intensity interval training and moderate-intensity continuous training groups. In the present study, our CR training program was effective in improving cardiorespiratory fitness (assessed as peak VO_2) and had similar results with FITR heart study.[13] In a previous prospective study, CR and exercise in patients with CAD after PCI reduced high-sensitive CRP (hsCRP) levels by 59.4% (p < 0.0001).[14] In patients with post-infarction HF, a 6-month intervention exercise training significantly reduced BNP levels compared with a control group.[15] The results of the present study were consistent with those of previous studies. The Emerging Risk Factor Collaboration (ERFC) reviewed 160,309 individuals from 54 prospective studies and found 27,769 patients who suffered from fatal or nonfatal events. Additionally, the previous study found that per 1-SD higher log_e CRP concentration was associated with an increased risk of CV events.[16] Each SD increase in log NTproBNP level (1.3 pg/mL) was associated with a 1.7-fold increased rate of adverse CV outcomes in stable patients with CAD.[17]

Table 1
Demographics of the study subjects (*n* = 23).

	N (%)
Age (years)	65 (56,75)
Male (%)	19 (82.6%)
DM (%)	3 (13.0%)
HTN (%)	21 (91.3%)
Smoking (%)[#]	6 (26.1%)
LVEF*	64.8 (56.0, 73.2)
Creatinine (mg/dL)*	0.95 (0.7, 1.2)
ALT (U/L)*	23 (20, 34)
Beta blocker (%)	14 (60.9%)
ACEI/ARB (%)	16 (69.6%)
Statin (%)	18 (78.3%)

ACEI: angiotensin converting enzyme inhibitor; ALT: alanine transferase; ARB: angiotensin II receptor blocker; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction.
* Express as median (interquartile range).
[#] Smoking status before stent deployment but quit smoking after participating the study.

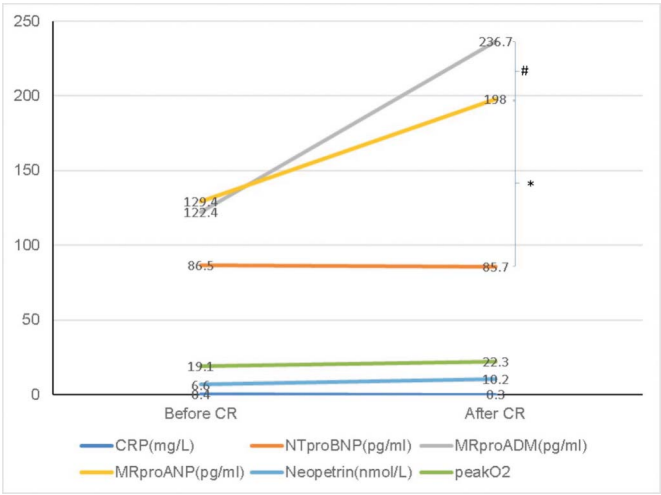

Figure 1. The dynamic change for all biomarkers and peak VO2 at baseline and 6 months after CR. Interaction with CR effect of change in MRproANP and MRproADM, NTproBNP levels was p < 0.001 and p = 0.05, respectively. * p < 0.001; [#] p = 0.05. Abbreviation as Table 2.

Table 2
Baseline and 6-month follow-up in patients with coronary artery disease.

	Before CR	End CR	p value
Peak VO_2 (ml/kg/minute)	19.1 (18.2, 22.3)	22.3 (20.0, 25.2)	< 0.001
Oxygen pulse (Peak VO_2/HR)	10.6 (9.7, 13.2)	10.9 (10.2, 13.3)	0.04
Workload (METs)	6.1 (5.4, 6.7)	6.4 (5.6, 7.2)	0.09
VE/VCO_2 slope	32.4 (30.0, 37.2)	32.7 (30.0, 37.2)	0.14
ST-2 (pg/mL)	217.0 (154.0, 366.0)	210.0 (161.0, 297.0)	0.59
CRP (mg/L)	0.4 (0.2, 0.7)	0.3 (0.1, 0.5)	0.006
NTproBNP (pg/mL)	86.5 (81.7, 106.4)	85.7 (79.9, 95.4)	0.017
MRproADM (pg/mL)	122.4 (96.2, 167.1)	236.7 (152.3, 300.7)	0.005
MRproANP (pg/mL)	129.4 (108.2, 163.9)	198.0 (156.5, 245.0)	< 0.001
Neopetrin (nmol/L)	6.6 (5.0, 9.8)	10.2 (8.7, 14.6)	< 0.001
LDL-C (mg/dL)	85 (63, 96)	86 (65, 106)	0.20
HDL-C (mg/dL)	40 (31,47)	36 (29, 44)	0.41

Present as median [interquartile range (Q1–Q3)].
CR: cardiac rehabilitation; CRP: C reactive protein; HDL-C: high density lipoprotein cholesterol; HR: heart rate; LDL-C: low density lipoprotein cholesterol; METs: metabolic equivalents; MRproADM: mid-regional pro-adrenomedullin; MRproANP: mid-regional pro-ANP; NTproBNP: N terminal pro B type natriuretic peptide; Peak VO_2: maximal oxygen uptake; ST-2: soluble suppressor of tumorigenicity 2; VE/CO_2 slope: minute ventilation/carbon dioxide production.

Therefore, the significant decrease in NTproBNP and CRP levels after CR represented the effectiveness of CR in our study.

In addition, we found that levels of other biomarkers including MRproANP, MRproADM, and neopterin were increased before and after CR. MRproANP potentially offers better prognostic utility than NTproBNP in patients with HF with preserved ejection fraction (HFpEF).[18] In our study, we found an-at first sight paradoxical-increased MRproANP level after a 6-month CR program. Increased MRproANP levels was considered an isolated marker that reflected increased left atrial wall stress. Nevertheless, when NTproBNP levels were taken into consideration, we hypothesized that in the presence of CAD with decreased NTproBNP, high levels of MRproANP after the 6-month CR program may indicate a functional left atrium rather than left atrial wall stress in our study. Patients with HFpEF had reduced active atrial contractile reserve than those with nonfailing hypertensive left ventricular hypertrophy.[19] Patients with mitral regurgitation and HF (NYHA class III/IV) had lower ANP levels than those with HF (NYHA class II);[20] this may indicate an association between lower ANP levels in severe HF and left atrial dysfunction. Increased ANP synthesis and storage in the myocardium and induced adaptive changes in the ultrastructure of cardiomyocytes were found in the rats trained by moderate and high exercise intensities.[21] There was borderline significant interaction between MRproANP and NTproBNP in our study. We speculated that there may be a different regulatory mechanism of MRproANP and NTproBNP secrection response to CR in patients with stable CAD. Furthermore, we strengthened its interaction as a target for future elucidation.

The levels of MRproADM increased after the 6-month CR program in our study. Subjects free of adverse CV events had higher ADM levels than those with adverse CV events in a long-term study in patients with chest pain/positive functional test under coronary angiography.[22] In a rat coronary ligation model, ADM administered immediately after a myocardial infarction improved survival, reduced oxidative stress, and ameliorated progression of left ventricular remodeling and HF.[23] Therefore, elevated ADM levels might have cardioprotective effects. In addition, a positive correlation between plasma ADM and ANP after a prolonged, moderate intensity dynamic exercise in healthy young men suggested that increased ADM and ANP secretion might be a compensatory mechanism, which attenuates increased BP and cardiac function deterioration.[24] Similarly, significant interaction between MRproADM and MRproANP levels after the 6-month CR program was found in our study.

One of our findings was a significant increase in neopterin levels after the 6-month CR program. Neopterin has long been known as a biomarker of inflammation and has been used as a predictive marker in CV risk assessment.[25] Recently, neopterin was found to suppress the formation of oxidized low-density lipoprotein-induced foam cell, the migration and proliferation of vascular smooth muscle cells (VSMCs), and the adhesion of monocytes to endothelial cells (ECs).[26] Neopterin has been demonstrated to stimulate inducible nitric oxide synthase gene expression and induce nitric oxide dependent apoptosis in the VSMCs of rats;[27,28] additionally, neopterin has been associated with plaque calcification and vascular remodeling.[29] These findings indicate that neopterin plays an important role in vascular remodeling. Injection of neopterin attenuated the development of atherosclerotic lesions, and infusion of anti-neopterin neutralizing antibodies accelerated the development of atherosclerotic lesions in Apoe-/- mice.[26] Neopterin production may contribute to atheroprotection.

In summary, CR had anti-inflammatory effect (CRP),[30] left ventricular remodeling (NTproBNP),[31] an improvement in endothelial-derived vasodilation (MRproADM),[32,33] increased antioxidant capacity (neopterin)[34,35] and might improve LA function (MRproANP). From a clinical perspective, these biomarkers in our study may provide insight into efficacy of CR as well as pathophysiological pathways involved in the beneficial effects of CR.

Our study had several limitations. First, this study was monocentric. However, the monocentric characteristic of the study allowed us to provide the patients with comparable and effective CR interventions performed by the same measuring equipment. Second, the sample size was small. We used a longitudinal, repeated measures study design in which each participant was treated as his own control to maximize the ability of finding a causal relationship between CR and biomarker release. Considering the limitations of our study, as it is a pre-post design study, the bias of regression to the mean should be considered. Without control group to compare against and less control of confounding variables, interpretation of our results should be cautious. However, the results of our study can serve as a direction for selecting biomarkers for future research. Third, women accounted for only 17.4% of the participants; therefore, the generalizability of our findings to both sexes should be studied further. Fourth, we did not have echocardiographic data after CR. Therefore, we cannot show the biomarker changes in line with echocardiographic parameters.

5. Conclusion

In conclusion, our study showed that a 6-month CR program increased the levels of biomarker (MRproADM and neopterin) involved in angiogenesis, antioxidation, and atheroprotection; however, NTproBNP and CRP levels were decreased. Our results indicated that CR might increase blood flow to the myocytes due to increased angiogenesis factors and may have an atheroprotective effect. CR had a positive effect in patients with CAD and should be considered as an effective nonpharmacological prevention method. Our study also highlighted the fact that different mechanisms lead to increases in different cardiac biomarkers after CR. Further studies are warranted to elucidate the physiological mechanism by which CR induces the secretion of these biomarkers.

Competing interests

The authors declare that there is no conflict of interest.

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