

The effect of home-based cardiac rehabilitation on arterial stiffness and peak oxygen consumption in patients with myocardial infarction

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Received: August 28, 2022 Accepted: March 22, 2023 Published online: June 13, 2023

ABSTRACT

Objectives: This study aims to investigate the effectiveness of home-based cardiac rehabilitation (CR) on arterial stiffness in patients with acute myocardial infarction (AMI).

Patients and methods: Between January 2015 and December 2017, a total of 135 patients (120 males, 15 females; mean age: 58.8±11.1 years) with AMI who were referred for CR were included. Home-based CR was prescribed based on a cardiopulmonary exercise test (CPET) for at least six months. All patients completed three consecutive CPETs and brachial-ankle pulse wave velocity (baPWV) measurements at one, four, and seven months after onset.

Results: After six months of CR, there was an improvement in peak oxygen consumption (pVO₂) (Month 1, 28.7±6.4 mL/kg/min; Month 4, 31.6±6.3 mL/kg/min; Month 7, 31.2±7.1 mL/kg/min, p<0.001) and a reduction in baPWV (Month 1, left, 1546.0±311.2 cm/sec, right 1545.5±301.5 cm/sec; Month 4, left, 1374.9±282.5 cm/sec, right 1371.6±287.5 cm/sec; Month 7, left, 1362.9±287.0 cm/sec, right 1365.5±281.1 cm/sec, p<0.001).

Conclusion: In patients with AMI, arterial stiffness and aerobic capacity improved after six months of home-based CR, particularly in the early stages of rehabilitation. These results suggest that changes in baPWV are useful in determining the effectiveness of CR and pVO₂ in the initial stages of CR.

Keywords: Arterial stiffness, home-based cardiac rehabilitation, myocardial infarction, peak oxygen consumption.

Acute myocardial infarction (AMI) is a type of coronary heart disease (CHD) and the leading cause of death in elderly. After successful acute treatment of AMI, cardiac rehabilitation (CR) is the most crucial component of management for secondary prevention and improvement of cardiorespiratory fitness.^[1] According to the American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines, CR is a crucial part of caring for CHD patients, and the concept of CR has been expanded to include not

only simple exercise-based rehabilitation, but also cardiovascular disease (CVD) risk factor management, education, and social support.^[1,2] The effectiveness and safety of medically-supervised center-based CR are well known.^[1] However, due to the low participation rate in this form of CR, home-based CR has been introduced.^[3] Previous studies have reported that there is no significant difference in outcomes between center-based and home-based CR,^[4,5] and this has led to the emergence and popularity of home-based CR.

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Cite this article as:

Lee SJ, Choi JH, Kim SY, Lee JG, Lee SY, Lee HJ. The effect of home-based cardiac rehabilitation on arterial stiffness and peak oxygen consumption in patients with myocardial infarction. Turk J Phys Med Rehab 2023;69(x):i-ix. doi: 10.5606/tftrd.2023.11637.

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The gold-standard test for determining functional capacity in patients undergoing CR is cardiopulmonary exercise test (CPET).^[6] It is a non-invasive method for evaluating the performance of the lungs and heart while exercising. Peak oxygen consumption (pVO_2) is measured and is a powerful predictor of long-term survival in individuals with CHD. Changes in the pVO_2 were used to measure the effectiveness of exercise therapy in patients with CR.^[7]

The risk of CVD is independently predicted by arterial stiffness.^[8] Aging, smoking, obesity, and other comorbidities such as diabetes, hypertension, and dyslipidemia decrease arterial elasticity and increase arterial rigidity.^[9,10] These changes in arterial wall tissue can be usually measured by pulse wave velocity (PWV), with a higher PWV implying more rigid arteries.^[11] The PWV is an accurate indicator of arterial stiffness and a predictor of mortality and CVD.^[12] It is known that arterial stiffness is improved by exercise.^[13,14] It can be inferred that arterial stiffness can be improved through exercise-based CR in AMI patients. Besides, it

can be expected to determine how effective exercise-based CR is by quantitatively measuring arterial stiffness using PWV. Many researches have been conducted to confirm the usefulness of PWV, but they have not shown consistent results.^[9,15-17] There is still insufficient evidence to use arterial stiffness to determine the effectiveness of CR in AMI patients.

In the present study, we aimed to evaluate the effectiveness of home-based CR on arterial stiffness and pVO_2 in AMI patients.

PATIENTS AND METHODS

This single-center, study was conducted at Jeju National University Hospital, Department of Cardiology between January 2015 and December 2017. Our center is one of 14 regional cardiocerebrovascular centers (RCC) in South Korea. Patients who were diagnosed with first-onset AMI and underwent percutaneous coronary intervention (PCI) were screened. Initially, if a patient with AMI symptoms visited the emergency room and was diagnosed with

TABLE 1
Risk assignment for cardiovascular complications that can develop with exercise

	Low-risk	Moderate-risk	High-risk
Ischemic	<ul style="list-style-type: none"> - Atherosclerotic factors(+) - CAD history without current ischemia or evidence of atherosclerosis within 1 year - Normal EST 	<ul style="list-style-type: none"> - Angina/ischemia at exercise of moderate to high intensity (>7METs) - Stable after an ischemic event, coronary artery bypass graft, or angiographic intervention - Controlled at medication with lower intensity exercises 	<ul style="list-style-type: none"> - Angina/ischemia at exercise of low intensity (<5 METs) - Complex coronary anatomy not amenable to revascularization or intervention
Arrhythmia	<ul style="list-style-type: none"> - Rate-controlled, Nonsustained supraventricular arrhythmias with no hemodynamic compromise - Unifocal, infrequent (<10%) premature ventricular contractions 	<ul style="list-style-type: none"> - Rapid supraventricular arrhythmias with or without symptoms but no hemodynamic compromise - Multifocal premature ventricular contractions, couplets, triplets, or history of nonsustained ventricular tachycardia - Those who have pacemakers 	<ul style="list-style-type: none"> - Hemodynamics compromise - Recent history of ventricular tachycardia, asystole, ventricular fibrillation - Those who have ICDs
Failed pump	<ul style="list-style-type: none"> - Distant history of CHF controlled with medications - Class I of NYHA - Left ventricular dysfunction (EF >50%) - With moderate intensity exercise, there is a normal or subtle rise (5-20 mmHg) in systolic blood pressure 	<ul style="list-style-type: none"> - Active CHF controlled with medications - Class II of NYHA - Left ventricular dysfunction (EF 40-50%) - No or little systolic blood pressure increase (0-5 mmHg) with mild to moderate intensity exercise 	<ul style="list-style-type: none"> - CHF at rest or with exercise of mild intensity - Class III or IV of NYHA - Left ventricular dysfunction (EF <40%) - Recent history of systolic blood pressure dropping during or just after exercise

CAD: Coronary artery disease; EST: Exercise stress test; MET: Metabolic equivalent; ICD: Implantable cardioverter defibrillator; CHF: Chronic heart failure; NYHA: New York Heart Association classification; EF: Ejection fraction.

AMI, they were admitted to the cardiology department for treatment such as PCI. After the patients were stabilized, they were referred from the cardiology department to the department of rehabilitation for CR. At one month after onset, the patients were evaluated for CPET or PWV through outpatient care at the department of rehabilitation before the start of CR. Based on the evaluation, patients were classified as low-risk, moderate-risk, and high-risk according to risk assignment for cardiovascular complications that can develop with exercise (Table 1).^[18] and individualized exercise prescriptions such as exercise method, exercise intensity, and frequency were given and home-based CR was initiated. Outpatient follow-up evaluation was conducted at four and seven months after the onset and the exercise prescription was adjusted based on each evaluation result.

Inclusion criteria were as follows: patients with AMI after PCI; AMI as the primary diagnosis; age ≥ 20 years; and agreed to CR and complete CR for six months. Exclusion criteria were as follows: uncontrolled cardiac arrhythmia, hypertension, or heart failure; inability to participate due to cognitive impairment or musculoskeletal problems; and undergoing cardiac surgery. A total of 242 patients were referred for CR during the study period. Fourteen patients with non-myocardial infarction (MI) were excluded, of which two had heart failure and 12 had valvular heart disease. Of the remaining 228 patients, 93 were excluded from the study. Of these, 71 patients refused to be enrolled in the study, 21 patients were lost to follow-up, and one patient received coronary artery bypass grafting (CABG). Finally, a total of 135 patients (120 males, 15 females; mean age: 58.8 ± 11.1 years) were included in the study (Figure 1). All participants were instructed to take the medications prescribed by a cardiologist.

Data collection

Baseline demographic data of all participants such as age and sex were obtained. Weight, height, and body mass index (BMI) were measured. The BMI was calculated by getting the weight in kg and dividing it by the height in meters squared. Disease-related characteristics such as comorbidities, and medications the patients were taking were recorded. The CPET and PWV were performed in all patients.

Cardiopulmonary exercise test

First, CPET was performed to measure pV_{O_2} after being referred from the Department of Cardiology to the Department of Rehabilitation Medicine. The resting heart rate (RHR), resting diastolic blood pressure (RDBP), resting systolic blood pressure (RSBP), maximal heart rate (MHR), maximal diastolic blood pressure (MDBP), maximal systolic blood pressure (MSBP), and duration and rate pressure product (RPP) were also measured at one, four, and seven months. The RHR and resting blood pressure (RDBP and RSBP) were measured after resting for approximately 5 min in a quiet environment.

According to the CPET findings, the patients underwent home-based CR for at least six months. The CPET and PWV were performed after one, four, and seven months, respectively, based on the onset of AMI.

Pulse wave velocity

The PWV includes the brachial-ankle PWV (baPWV), carotid-femoral PWV (cfPWV), and femoral-ankle PWV (faPWV). Dividing into segments, cfPWV is mainly used for central PWV and faPWV is used for peripheral PWV. The baPWV is used to check composed peripheral and central arterial stiffness and is mainly used in Korea and Japan.^[13-15] In this study, VP 1000 Plus

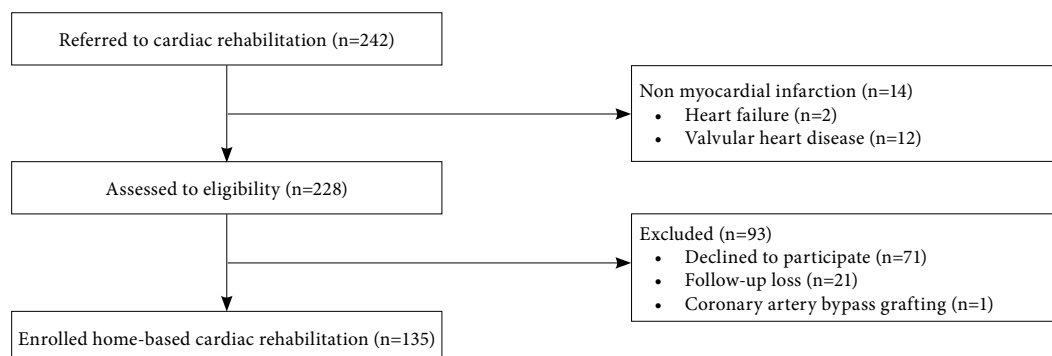


Figure 1. Study flowchart.

(Omron Colin Company, Japan), an automated waveform analyzer, was utilized by qualified technicians to measure the baPWV for the right side (right brachial, right ankle) and the left side (left brachial, left ankle). Using formulae based on height, VP 1000 plus automatically determined the distance for baPWV. Before measuring baPWV, the patients relaxed in the supine posture for approximately 5 min.

Cardiac rehabilitation program

The CR program includes patient education, evaluation, and exercise training. Education was mainly provided for risk factor management, such as diet, management of stress, and smoking cessation. For patient evaluation, CPET, PWV, ankle-brachial index (ABI), and body composition analysis were performed in the outpatient clinic. In home-based rehabilitation, the recommended exercise intensity for each individual was presented as a target heart rate according to the CPET results. Patients who were in high-risk group according to risk assignment for cardiovascular complications that can develop with exercise underwent center-based CR before home-based CR. Through center-based CR, the participants were monitored during exercise and it was ensured that they did not have a serious problem during exercise. Afterwards, home-based CR was conducted. The target heart rate corresponded to 40 to 80% of the maximal fitness level obtained through CPET. The

exercise was performed at least five times a week for at least 30 min per day. Warm-up exercises, such as stretching, were performed before exercise and low intensity finishing exercises were performed after exercise. The patients performed aerobic exercises using a treadmill, outdoor walking, or running. They were provided with a fitness band to check their heart rate. They wore a fitness band, which helped them to exercise at the suggested target heart rate in real time. After the exercise, they were instructed to record the exercise time and frequency in their exercise notes, and the physician monitored them at the time of hospital visit.

Statistical analysis

Statistical analysis was performed using the PASW for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented in mean \pm standard deviation (SD), while categorical variables were presented in number and frequency. Repeated-measures analysis of variance (ANOVA) was used to analyze changes in the variables that were measured. Once confirmed to be statistically significant by repeated measures ANOVA, the Bonferroni correction was used as a post-hoc test, and it was possible to reduce the type 1 error and specifically to confirm whether baPWV changed with CR. A p value of <0.05 was considered statistically significant.

Variables	n	%	Mean \pm SD
Age (year)			58.8 \pm 11.1
Sex,			
Males	120	88.9	
Females	15	11.1	
Height (cm)			165.7 \pm 8.7
Weight (kg)			69.8 \pm 12.4
Comorbidities			
Hypertension	64	47.4	
Diabetes mellitus	32	23.7	
Dyslipidemia	33	24.4	
Heart failure	5	3.7	
Medication			
Beta blocker	117	86.7	
ACEi/ARB	66	48.9	
Calcium channel blocker	13	9.6	
Diuretics	13	9.6	

SD: Standard deviation; ACEi: Angiotensin converting-enzyme inhibitor; ARB: Angiotensin receptor blocker.

RESULTS

During the home-based CR, no exercise-related problem such as life-threatening arrhythmias or chest pain occurred in any patients. Disease-related characteristics and demographic data of the patients are shown in Table 2.

Changes in anthropometrics, baPWV, resting hemodynamics, and cardiopulmonary fitness at one, four, and seven months are shown in Table 3. There were significant improvements in pVO_2 (Month 1, 28.7 ± 6.4 mL/kg/min; Month 4, 31.6 ± 6.3 mL/kg/min; Month 7, 31.2 ± 7.1 mL/kg/min, $p < 0.001$), and

TABLE 3 Changes in anthropometrics, brachial-ankle pulse wave velocity, resting hemodynamics and cardiopulmonary fitness						
Variables	Time	RM-ANOVA		p-value by Bonferroni correction		
		Mean \pm SD	<i>p</i>	a vs. b	a vs. c	b vs. c
Body mass index	a. 1 month	25.7 \pm 2.7	0.156			
	b. 4 months	25.2 \pm 3.0				
	c. 7 months	25.3 \pm 2.6				
baPWV(cm/sec)-right	a. 1 month	1545.5 \pm 301.5	<0.001	<0.001	<0.001	1.0
	b. 4 months	1371.6 \pm 287.5				
	c. 7 months	1365.5 \pm 281.1				
baPWV (cm/sec)-left	a. 1 month	1546.0 \pm 311.2	<0.001	<0.001	<0.001	1.0
	b. 4 months	1374.9 \pm 282.5				
	c. 7 months	1362.9 \pm 287.0				
pVO_2 (mL/kg/min)	a. 1 month	28.7 \pm 6.4	0.003	<0.001	0.066	1.0
	b. 4 months	31.6 \pm 6.3				
	c. 7 months	31.2 \pm 7.1				
Duration (sec)	a. 1 month	839.5 \pm 189.1	0.207			
	b. 4 months	979.8 \pm 1084.0				
	c. 7 months	809.4 \pm 240.3				
RPP (mmHg \times beats/min)	a. 1 month	23246.4 \pm 5652.8	0.330			
	b. 4 months	24100.3 \pm 4917.5				
	c. 7 months	23727.8 \pm 6098.5				
MHR (beats/min)	a. 1 month	146.3 \pm 21.8	0.466			
	b. 4 months	149.0 \pm 21.1				
	c. 7 months	146.8 \pm 24.3				
MSBP (mmHg)	a. 1 month	158.4 \pm 28.1	0.045	0.021	0.295	1.0
	b. 4 months	163.9 \pm 23.1				
	c. 7 months	162.5 \pm 25.4				
MDBP (mmHg)	a. 1 month	74.1 \pm 12.4	0.052			
	b. 4 months	75.8 \pm 12.5				
	c. 7 months	78.1 \pm 14.9				
RHR (beats/min)	a. 1 month	78.6 \pm 13.2	0.026	0.067	0.057	1.0
	b. 4 months	75.8 \pm 13.5				
	c. 7 months	75.5 \pm 13.7				
RSBP (mmHg)	a. 1 month	119.1 \pm 16.1	0.358			
	b. 4 months	127.6 \pm 75.3				
	c. 7 months	119.5 \pm 15.4				
RDBP (mmHg)	a. 1 month	72.3 \pm 11.5	0.463			
	b. 4 months	72.7 \pm 10.9				
	c. 7 months	72.6 \pm 11.0				

SD: Standard deviation; RM-ANOVA: Repeated measured analysis of variance; baPWV: Brachial-ankle pulse wave velocity; pVO_2 : Peak oxygen consumption; RPP: Rate pressure product; MHR: Maximal heart rate; MSBP: Maximal systolic blood pressure; MDBP: Maximal diastolic blood pressure; RHR: Resting heart rate; RDBP: Resting diastolic blood pressure; RSBP: Resting systolic blood pressure.

a significant reduction in baPWV (Month 1, left, 1546.0 ± 311.2 cm/sec, right 1545.5 ± 301.5 cm/sec; Month, left, 1374.9 ± 282.5 cm/sec, right 1371.6 ± 287.5 cm/sec; Month 7, left, 1362.9 ± 287.0 cm/sec, right 1365.5 ± 281.1 cm/sec, $p < 0.001$). There were no significant differences in BMI, MHR, MDBP, RSBP, RDBP, duration, and RPP.

DISCUSSION

In the present study, we found that home-based CR was effective in lowering arterial stiffness and increasing pVO_2 in AMI patients. The main finding of this study was that there was a significant improvement in PWV between one and four months. Several studies have supported this finding and have confirmed that rehabilitative exercise for a short period (<20 weeks) leads to improvement in PWV.^[15-17] On the contrary, a study by Oliveira et al.^[9] reported that eight weeks of exercise-based CR was not sufficient in decreasing PWV and did not affect arterial stiffness or other inflammatory biomarkers in patients with MI. Although there was a significant improvement in the *per protocol* analysis, they suggested that this was false positivity due to the many comparisons performed. It is important to note, however, that in our study, patients exercised at least five times a week, compared to the thrice-week exercise performed by the participants in their study. We believe that this difference in the amount of exercise may be responsible for the different results of our study compared to their study.

In the current study, we showed that PWV significantly improved in early stages of home-based CR, but there was no significant improvement in PWV after early stage. Based on these findings, we can speculate that home-based CR is mostly beneficial in the early stage. The pVO_2 results also showed a significant improvement only in early stage. It can be inferred that this result is similar to that of PWV. Taken together, it was possible to indirectly infer that pVO_2 and PWV had a coidentity as an index of the effectiveness of CR.

Few studies have described the long-term effects of home-based CR. In the study of Trzos et al.,^[17] PWV values of the exercise group were maintained below their baseline levels, whereas the control group showed a little improvement after more than six months. However, the mean period of post-hospital rehabilitation in the study was only six weeks, and examination was performed six months after the end of the exercise program. In the study of Laskey

et al.,^[16] a dose-response relationship was observed between the decrease in PWV and the quantity of CR sessions, but the authors only compared the results of the 12-week versus 20-week exercise programs. The maximum period of CR was only 20 weeks. This study is different with studies of Trzos et al.^[17] and Laskey et al.^[16] in that the patients continued the exercise program for seven months. To confirm whether CR is effective in the after early phase, more research is needed regarding the long-term effects of home-based CR.

The importance of CR in patients with CHD has been established. Many clinical studies have confirmed that CR provide a decrease in both cardiac and all-cause mortality rates.^[19-21] Furthermore, the number of CR sessions and long-term mortality outcomes are significantly correlated in a dose-response manner.^[22] The second phase of CR leads to improved exercise tolerance and improved general physical and mental states.^[23-25] Exercise enhances vascular function through the bioavailability and production of nitric oxide, which is anti-atherogenic. It directly affects the remodeling of arterial structure, improves wall-to-lumen ratios, and increases arterial caliber.^[26] Furthermore, no distinction has been shown between the results of center-based and home-based rehabilitation.^[4,5] Therefore, the importance of home-based CR in terms of medical expenses and efficacy is emerging. In this study, fitness bands and exercise notes were used to check compliance in patients with home-based CR.

The utility of pVO_2 has been proven in several studies where it was used to measure the peak aerobic capacity and effectiveness of CR.^[27,28] Additionally, pVO_2 is an independent and significant predictor of cardiovascular and all-cause mortality, including MI.^[7,29] However, to measure pVO_2 , a CPET test is necessary, and it is relatively difficult to perform unless the patient is in the condition to exercise. In addition, it has the disadvantage of requiring sophisticated equipment and substantial technician. Comorbidities such as pulmonary disease can also affect the result of tests. On the other hand, PWV has also the possibility of being method to measure exercise capacity since the key factor affecting exercise capacity is arterial distensibility because a higher cardiac workload results from increased arterial stiffness,^[17] and is relatively easy to test and less affected by ventilation problems. In addition, PWV has the advantage of being able to determine the degree of vascular atherosclerosis. Therefore, PWV can be a good choice as an alternative method.

The PWV is important, due to its usefulness in evaluating arterial stiffness and predicting mortality. It has been used as a tool for evaluating arterial stiffness and is considered an independent predictor of cardiovascular mortality. In a study by Laurent et al.,^[30] the risk coefficient for cardiovascular mortality was higher, when the value of PWV was higher by 5 m/sec.

The PWV can be divided into central (cfPWV), peripheral (faPWV), and composite (baPWV) PWV categories. An increase in thoracic aortic stiffness causes a rise in systolic blood pressure and a fall in diastolic blood pressure, leading to reduced blood flow to the coronary arteries, which is highly correlated with CVD.^[31] Many studies have shown that cfPWV and arterial stiffness are related and cfPWV can be used as a marker of cardiovascular risk.^[32-35] Currently, most Western countries have mainly used the cfPWV. However, for the testing to be widely used, it must be simple, convenient, and reproducible. Although cfPWV is a reference technique for evaluating arterial stiffness, it has some drawbacks, such as revealing the inguinal region. Besides, carotid and femoral pulse recording require technological expertise. Therefore, baPWV is an alternative index that has been more commonly used than the cfPWV, particularly in Eastern countries.^[10,35] The baPWV has a central arterial stiffness component, as well as a peripheral arterial stiffness component.^[36] Therefore, it has a strong positive association with cfPWV and the potential to identify the risk of CVD.^[31,35,37] Furthermore, in addition to the decrease in cfPWV after CR, a decrease in carotid-radial PWV, an indicator of peripheral arterial stiffness, was recently found.^[16] We conclude that baPWV can be a useful tool for evaluating the effectiveness of CR.

The effectiveness of CR appears to be influenced by multiple factors, including lifestyle modification, pharmacotherapy, and control of the underlying disease. Some antihypertensive drugs may have beneficial effects on arterial mechanical properties, resulting in lower PWV.^[38,39] While there are many studies on the effectiveness of medication-based treatment on arterial stiffness, it has been hard to disentangle the effectiveness of CR from the effectiveness of drugs, which particularly lower blood pressure. Most patients in this study were prescribed antihypertensive drugs, but there was no significant change in RBP. Similar results were reported in the studies of Tanaka et al.^[14] and Laskey et al.^[16] Furthermore, Trzos et al.^[17] showed that CR might be effective in improving arterial

stiffness, regardless of pharmacotherapy, in a case-control study. Therefore, we consider the results of this study to be due to exercise therapy, regardless of pharmacotherapy.

In this study, all patients underwent home-based CR and were managed with exercise notes. Nonetheless, this study has several limitations. First, the physician did not directly watch the patient performing the exercise and, thus, could not determine whether the patient exercised properly. Second, the patients were not investigated for respiratory disease associated with impaired ventilation or gas exchange. Since these respiratory diseases can affect the result of CPET, it can be a limitation of this study. More importantly, this study did not compare different patients, but conducted CPET over time in the same patient to evaluate changes in exercise capacity and PWV following home-based CR. Management and medication of underlying diseases such as respiratory diseases were continued to minimize the impact of CR. Third, although improvement of arterial stiffness between one month and four months, corresponding to the early stage of home-based CR, was confirmed, the long-term effectiveness of home-based CR was unable to be evaluated. Therefore, further long-term follow-up studies are needed to investigate the effectiveness of CR after seven months and how long home-based CR is effective in improving arterial stiffness. Finally, the baPWV distance is calculated using height-based formulas and, therefore, there may be a difference between the value of the actual anatomical distance and the value from height-based formulas. However, baPWV calculated using magnetic resonance imaging-based route length was linearly associated with baPWV calculated using height-based formulas. Therefore, the baPWV calculated using height-based formulas is clinically effective, particularly in terms of prognostic factors.^[37,40]

In conclusion, our study results showed that arterial stiffness and aerobic capacity were significantly improved after >6 months of home-based CR in AMI patients, particularly in the early stage of home-based CR. These results suggest that measured changes in baPWV can determine the effectiveness of CR, as well as pVO₂ at least in the early stages of home-based CR. Therefore, it is recommended to measure changes in arterial stiffness using PWV along with pVO₂ measurement in the early stages of home-based CR after MI. Further studies are warranted to explain why pVO₂ and arterial stiffness are not further improved after early stage.

Ethics Committee Approval: The study protocol was approved by the Institutional Review Board (IRB) of Jeju National University Hospital (date: 20.08.2020, IRB no: 2020-01-007). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design: J.H.C.; Control/supervision, analysis, writing the article, critical review, references and fundings, materials: J.H.C., S.J.L.; Data collection: J.H.C., S.Y.K., J.G.L., S.Y.L., H.J.L.; Literature review: S.J.L., J.H.C., S.Y.K., J.G.L., S.Y.L., H.J.L.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This work was supported by a research grant from Jeju National University Hospital in 2020

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