Current Status and Future Directions for Cardiac Rehabilitation in Japan

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The prevalence of coronary artery disease (CAD) has increased over the last several decades in Japanese population. Recent epidemiological studies have indicated that the incidence of acute myocardial infarction (MI) has increased, particularly in the urban areas of Japan. Previous data have strongly supported the important role of lifestyle intervention, including physical activity and dietary modification to improve glucose and insulin homeostasis, lipid profiles, and other risk factors for the prevention of CAD. Cardiac rehabilitation (CR) is a comprehensive intervention that includes supervised exercise training, risk factor control, patient education, and psychosocial counseling. CR has been reported to be effective in reducing the risk of cardiovascular events through intensive lifestyle modification. However, the implementation of CR is still low even in academic cardiovascular institutes. In this review, we will discuss the recent status and problems regarding the safety and efficacy of CR and will discuss the future directions of CR in patients with CAD in Japan.

Key words: cardiac rehabilitation, cardiovascular disease, diabetes mellitus, elderly patients, frailty

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. Approximately 42,000 Japanese people die of myocardial infarction (MI) every year1). Recently, patients with CAD have been treated with medical therapy with lifestyle modification, and coronary revascularization procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Although the recent progress of medical therapy and coronary revascularization is remarkable, implementation of cardiac rehabilitation (CR), a powerful methodology for lifestyle modification, appears to be yet unsatisfactory. In this review, we will discuss the recent status, problems, and the future directions of CR in patients with CAD in Japan.

Establishment of CR

In the 1930s, Mallory et al reported the pathological healing process after an acute MI and clearly showed that the period from acute myocardial necrosis to stable scar formation was more than 6 weeks. Therefore, in order to prevent ventricular aneurysm formation, heart failure, rupture and sudden death, bedrest for 6-8 weeks was practiced after acute MI, which, however, induced physical deconditioning and frequent pulmonary thromboembolism. Thus, the likelihood of returning to a normal social life had been relatively low2). In 1970s, before the wide utilization of coronary interventions, several studies demonstrated the better prognosis in patients with CAD who participated in a CR program. Thereafter the wide acceptance of PCI, Hambrecht et al reported that an exercise-training group with stable angina pectoris had an improved event-free survival at a 12-month follow-up compared with the PCI group3). A meta-analysis has shown that CR decreased the all-cause mortality by 20% and cardiac mortality by 25%4).

Comprehensive CR program for patients with CAD contains exercise and patient education and
counseling after ACS, CABG, and heart failure. CR is included as a class I recommendation in most contemporary cardiovascular clinical practice guidelines (Figure-1).

**Trends in risk profiles of patients with coronary artery disease in Japan**

Japan is a country with one of the fastest-aging populations. In addition, the prevalence of coronary risk factors in patients with CAD has increased due to the westernization and urbanization of lifestyles. We analyzed the data from the Juntendo PCI Registry, which consisted of the information regarding patients who underwent a PCI at Juntendo University Hospital from January 1984 to February 2010. The patients were divided into three groups according to the date of the index PCI procedure (plain old balloon angioplasty (POBA)-era, January 1984–December 1997; bare-metal stents (BMS)-era, January 1998–July 2004; and drug-eluting stents (DES)-era, August 2004–February 2010). A total of 3,831 patients were examined (POBA-era, n=1,147; BMS-era, n=1,180; DES-era, n=1,504). The mean age was highest during the DES-era. A higher prevalence of diabetes and hypertension was observed in the DES- and BMS-eras than in the POBA-era. These data clearly demonstrated that the patients became older and had higher risk, however, the control of major coronary risk factors has been insufficient and the need for CR is growing particularly among high risk population.

**Exercise as vascular medicine**

Exercise exerts beneficial effects on blood vessels and suppresses the progression of coronary atherosclerosis. Furthermore, the endothelial function of coronary arteries improved by regular exercise in patients who had MI. Another explanation for atherosclerotic plaque change could be improvements in vascular inflammation. Regular physical exercise has been associated with the decrease in inflammatory markers and ischemic events in patients with CAD. We also found that CR for 6 months ameliorated inflammatory states in patients with metabolic syndrome after CABG.

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**Figure-1** Current status and directions of CR

CR has been found to improve recurrence prevention and incidence prevention of cardiovascular disease after deconditioning after bed rest. (Goto Y: J Jpn Coron Assoc, 2015; 21: 56-66. modified)
voluntary exercise improved the progression of endothelial dysfunction and atherosclerotic lesion formation through anti-inflammatory effects in an experimental study\textsuperscript{11}. The regression of coronary atherosclerotic lesions has been shown by angiography in patients with CAD who expended an average of 2,200 kcal/week by physical exercise\textsuperscript{12}. Recently, we determined the effects of Phase II (PII) comprehensive CR on coronary plaque volume in patients after ACS. We assigned 46 patients with ACS into groups of patients who proceeded with PII-CR (PII-CR; n = 21) or those who did not (non-PII-CR; n = 25). Although risk factors, muscle strength, and exercise tolerance were improved by PII-CR, plaque regression did not significantly differ between the two study groups. However, a significant correlation between percent change in coronary plaque volume and physical activity was observed (Figure-2). A comprehensive PII-CR program, including frequent supervised exercise sessions and an agenda that encouraged increased physical daily activities, may reduce plaque volume in patients after ACS\textsuperscript{13}.

**Effects of CR in DM patients with CAD**

Patients with DM are at a 2–4 times higher risk of developing CAD and mortality due to CAD compared with patients without DM\textsuperscript{14}\textsuperscript{15}. The benefits of revascularization are less, whereas the risks and complications are higher than those in patients without DM. Previous studies have also reported a high incidence of bypass graft dysfunction and high mortality even in patients with DM who underwent CABG\textsuperscript{16}.

Improvement in peak VO\textsubscript{2} after CR decreased cardiovascular morbidity and mortality in patients with CAD\textsuperscript{17}. However, a previous study demonstrated that the presence of DM was a negative factor for the improvement in peak VO\textsubscript{2}\textsuperscript{18}. Another report showed a significant inverse relationship between fasting blood glucose levels and changes in peak VO\textsubscript{2} in CR participants with DM after coronary events\textsuperscript{19}. Park et al reported that low muscle strength was a predictor of physical limitations and that DM was associated with low skeletal muscle strength and deterioration in quality\textsuperscript{20}. We recently reported that muscle strength and exercise tolerance were significantly lower in patients with DM than in patients without DM at the beginning of CR after CABG\textsuperscript{21}. We had enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG (DM group, n = 37; non-DM group, n = 41). At the beginning of CR, muscle strength and peak VO\textsubscript{2} were significantly lower in the DM group than in the non-DM group. At the end of CR, significant improvement in muscle strength and exercise tolerance was observed in both groups. However, muscle strength, peak VO\textsubscript{2}, thigh circumference, and mid–upper arm muscle

\begin{figure}
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Correlations between percent change in plaque volume and physical activity (A) and exercise tolerance (B). Percent change in plaque volume inversely correlates with physical activity ($r = -0.48$, $p = 0.01$), but not with exercise tolerance ($r = 0.15$, $p = $NS). Reproduced with permission from Nishitani-Yokoyama M, et al: Int Heart J, 2015; 56: 597–604\textsuperscript{13}.}
\end{figure}

% P vol, ratio of change in plaque volume.
area (MAMA) were significantly lower in the DM group than in the non-DM group (Figure-3). In addition, no significant improvement in thigh circumference and MAMA was observed in the DM group. At the end of CR, thigh circumference and MAMA correlated with muscle strength. The percent changes in muscle strength were significantly correlated with those in MAMA and hemoglobin A1c. These data suggest that improvements in muscle strength are influenced by changes in muscle mass and high glucose levels in patients with DM undergoing CR after CABG. A CR program, including muscle mass intervention and blood glucose control, may improve deterioration in exercise tolerance in patients with DM after CABG. Armstrong et al reported that patients with DM who completed CR derived similar apparent reductions in mortality and hospitalization compared with patients without DM.

**Efficacy of CR in elderly patients with stable CAD: Juntendo Cardiac Rehabilitation Program (J-CARP) study**

As described above, the rate of aging is the highest in Japan. The MIYAGI-AMI Registry Study demonstrated that the overall age-adjusted incidence of acute MI (/100,000 persons/year) markedly increased by 3.6-fold, from 7.4 in 1979 to 27.0 in 2008 (p < 0.001). The number of elderly acute MI patients in Japan has dramatically increased over the past 30 years, particularly that of ≥80 year-old patients, of both sexes (both p < 0.001).
Elderly patients have a 2- to 3-fold higher incidence of acute MI compared with younger persons. They also have more complications, resulting in prolonged hospital stays with lower physical function and substantially higher fatality rates after CAD events. Because of this high rate of mortality and morbidity, primary and secondary prevention strategies are important approaches not only to improve survival but also to maintain the active social life of the elderly population. The benefits of CR have been reported in elderly and in younger patients. A recent report suggested that elderly patients have not been referred to or vigorously encouraged to attend these programs.

In general, CR programs are performed in three stages: acute stage (phase I), subacute stage (phase II), and chronic stage (phase III) (Figure-4). In Japan, most CR programs have been performed in phase I and some in phase II (26), however, phase III CR programs have not been performed often because they were not covered by Japanese health insurance until March 2006. We previously reported a phase III CR program called the Juntendo Cardiac Rehabilitation Program (J-CARP). Thirty-four male patients CAD (> 65 years old) were randomly assigned to an intervention group (n = 18) or a control group (n = 16). The intervention group participated in a phase III CR program consisting of exercise training, diet therapy, and weekly counseling for 6 months. In the control group, usual outpatient care was provided. In the intervention group, body mass index, waist size, and fat weight significantly decreased, the peak VO2 and anaerobic threshold VO2 were maintained, and muscle strength significantly improved. In the control group, all parameters were unchanged except for peak VO2, which significantly decreased. In the intervention group, serum total cholesterol levels significantly decreased after CR. However, high-density lipoprotein- cholesterol and apoA-I levels also decreased. In the control group, no significant change in lipid profile was observed.

Validated questionnaires were obtained to evaluate the health-related quality of life (QOL) using the
medical outcome study 36-item short-form health survey (SF-36), State-Trait Anxiety Inventory questionnaire (STAI) and self-rating depression scale (SDS) at baseline and after 6 months. At baseline, the scores of SF-36, except for general health, STAI, and SDS were not different in either group. After 6 months, in the intervention group, the scores of bodily pain, general health, vitality, and mental health of SF-36 improved significantly compared with the baseline levels. The state anxiety scores also significantly improved (p < 0.01), but SDS depression scores did not improve. In the control group, none of the parameters significantly changed.

In the next study, we assessed the effects of phase III comprehensive CR on the morbidity and mortality of elderly male Japanese patients with CAD. The 111 elderly male patients with CAD (≥65 years), including 37 subjects that participated in supervised CR for 6 months and 74 age-matched controls, were analyzed. The patients were followed for up to 3,500 days until the occurrence of death or one of the following major adverse cardiovascular events (MACE): cardiovascular death, ACS, refractory angina requiring revascularization, admission for congestive heart failure, or stroke. All-cause mortality tended to be lower in the CR group than in the control group (14% vs 28%, p = 0.081). MACE incidence was significantly lower in the CR group than in the control group (30% vs 62%, p = 0.001). The multivariate Cox proportional hazard analysis showed that MACE incidence was significantly lower in the CR group than in the control group [adjusted hazard ratio, 0.43 (95% confidence interval, 0.20–0.91), p = 0.027] (Figure 5).

The J-CARP study has demonstrated that phase III comprehensive CR program even in elderly patients with stable CAD improved physical fitness, coronary risk factors, QOL, anxiety, and clinical prognosis.

**Emerging risk of cardiovascular disease: frailty**

CAD is one of the diseases that leads to a decrease in the QOL of elderly patients and is the leading cause of morbidity and mortality. Frailty was defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (>4.5 kg in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Frailty is an important risk factor for CAD. Sergi et al demonstrated that pre-frailty, which could be potentially reversible, was independently associated with a higher risk of older adults to develop CAD. Among the physical domains of pre-frailty, low gait speed appeared to be the best predictor of
Recent European Society of Cardiology (ESC) guidelines have shown that CR is one of the treatment strategies for subjects with frailty. Bipolarization of patients with cardiovascular disease has been differentiated into “low-risk patients” and “high-risk patients” based on their clinical backgrounds. “Low-risk patients” have been characterized as young patients with preserved cardiac function and no residual lesions after coronary revascularization. “High-risk patients” needed multidisciplinary strategies to prevent re-hospitalizations and to preserve QOL.

Bipolarization of patients with cardiovascular disease in Japan

It has been reported that the patients with CAD have been differentiated into “low-risk patients” and “high-risk patients” based on their clinical backgrounds. “Low-risk patients” have been characterized as young patients with preserved cardiac function and no residual lesions after coronary revascularization. “Low-risk patients” had insufficient motivation for secondary prevention and often discontinued their CR participation because of early hospital discharge and an early return to work. They often have a high prevalence of smoking, dyslipidemia, and multiple coronary risk factors. Therefore, secondary prevention and life modification are strongly required. “High-risk patients” have been characterized as older patients with a high prevalence of heart failure, low cardiac function, and multiple comorbidities (e.g., chronic renal failure, diabetes, anemia, or cerebrovascular disease). They also require long-term disease management to prevent re-admission and to preserve QOL. It is important to participate in a comprehensive CR program after discharge. Individualized programs are often required (Figure 6).

Kamakura et al demonstrated that even in “low-risk patients” (<65 years old, successful reperfusion, Killip class I, peak serum creatine kinase < 6,000 U/L, and left ventricular ejection fraction ≥ 40%), active participation (≥20 sessions/3 months) in a PII out-patient CR program has been associated with improved exercise capacity and a better coronary risk factor profile.

Poor implementation of CR in Japan

Recently, the length of hospital stay for patients with acute MI has been substantially shortened, because emergency PCI enables early ambulation. This shortening of hospitalizations has made it difficult to initiate the in-hospital CR program with exercise training and patient education during the in-patient period, but outpatient CR programs do not appear to be widely used.

The Japanese CR Survey demonstrated that the rates of implementation of emergency PCI were very high (92% of Japanese Circulation Society training hospitals) and that the rates of implementation of recovery phase CR were low (20% of the Japanese Circulation Society training hospitals). In addition, the patient education programs (23% of
the Japanese Circulation Society training hospitals) and formulated exercise prescriptions based on exercise testing (16% of the Japanese Circulation Society training hospitals) were poorly implemented. More importantly, only 9% of these hospitals had outpatient CR programs. The nationwide participation rate in outpatient CR after acute MI in Japan was estimated to be only 3.8%–7.6%. 

The implementation of recovery phase CR, particularly as outpatient CR, is extremely poor in Japan. In addition, patient education programs and exercise prescriptions based on exercise testing have been poorly implemented. The benefits of CR have been established, therefore, it is necessary to improve the spread of recovery-phase and outpatient CR in Japan.

Conclusions

It is clear that CR improves exercise capacity, QOL, risk factors, and prognosis for patients with CHD. However, the use of outpatient CR programs after hospital discharge remains particularly insufficient in Japan. In addition, it is important to establish CR programs for elderly patients, patients with DM and subjects with frailty. Future studies and social capital supports are required to resolve those problems.

Disclosures

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