Chapter 2
Exercise Exerts Its Beneficial Effects on Acute Coronary Syndrome: Clinical Evidence

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Abstract Acute coronary syndrome (ACS) is characterized with high morbidity, high mortality, long hospitalization and frequent revisits. It has been the most serious coronary artery diseases in the world. A large body of clinical evidence demonstrates that exercise is associated with reduced cardiovascular disease risk. In addition, different types of exercise have become the central to most cardiac rehabilitation/risk reduction programs. However, the detailed effects of exercise in ACS is still unclear and there is still lack of evidence on which exercise regimen may be ideal for ACS. This chapter presents a brief review of the pathophysiology of ACS and the relationship between exercise and the cardiovascular system. Besides that, this chapter also provide an updated discussion of the most relevant discoveries regarding to exercise and its role in managing ACS in clinical studies.

Keywords Acute coronary syndrome • Exercise • Cardiovascular disease • Clinical evidence

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1 Introduction

Coronary artery disease remains the first cause of mortality worldwide [1]. Coronary artery disease contributes to the major cause of cardiovascular mortality, being responsible for approximately seven million of deaths [2]. Among all types of coronary artery diseases, acute coronary syndrome (ACS) is the most serious one. Each year in America, there are approximately 635,000 new diagnosed ACS patients [3–8]. It is also associated with longer hospitalization and more frequent revisits [9, 10].

Although the mortality of ACS has declined substantially [11], the situation stays critical. It is estimated that 40% of patients who experience a coronary event will have increased risk of death within 5 years but the risk can be 5–6 times higher in individuals who experience a recurrent event [12–14]. The economic burden due to ACS is also quite huge. The cost of one patient in 1 year is estimated to be from US$22528 to US$32345. The majority of the cost is due to hospitalizations [15, 16]. Given its deleterious impact on health economic consequences, it has been required to have evidence-based management for these patients.

ACS refers to the dysfunction of cardiac muscle due to decreased blood flow in the coronary arteries [17]. ACS is usually divided into three categories: ST elevation myocardial infarction (STEMI, 30%), non ST elevation myocardial infarction (NSTEMI, 25%), or unstable angina (38%) [18]. Physical well-being may improve cardiac-related outcomes [19]. Back into the early 1950s, standard treatment of myocardial infarction (MI) was several weeks of hospitalization followed by months of restriction of physical activity [20]. Exercise-based cardiac rehabilitation was developed to reverse the physical deconditioning produced by this restriction of physical activity [21]. Exercise training is central to most cardiac rehabilitation/risk reduction programs. It decreases the risk of coronary artery disease (CAD) [22–25], slows the progression of CAD [26, 27], increases exercise capacity and reduces exercise-induced cardiac ischemia [28].

Different types of exercise have been applied and they come with various protocols in cardiac rehabilitation [29, 30]. Despite this, there is still lack of evidence on which exercise regimen may be ideal for ACS [31]. Therefore, more attention should be paid to verify this.

In this chapter, we will present a brief review of the pathophysiology of acute coronary syndrome and the relationship between exercise and the cardiovascular system. We will also provide an updated discussion of the most relevant discoveries regarding to exercise and its role in managing ACS in clinical studies.

2 Pathophysiology of Acute Coronary Syndrome

Coronary artery disease is characterized by the formation of an atherosclerotic plaque following a long-term and complex process [32]. Most of the time patients would remain asymptomatic if the plaque is stable. Once ruptures, it can cause partial or complete occlusion of a coronary artery. The rupture of plaque exposes the collagen underneath the endothelial, which may result in cascade of platelets activation, leading to thrombus formation [33]. The reduction of blood flow results in these typical angina symptoms [34, 35].

Patients with complete occlusion generally present with STEMI [36]. If the occlusion is unresolved in a timely manner, it may result in transmural infarction [37]. This provides the rationale for early reperfusion with either pharmacological or catheter-based approaches. Patients with partially occluded coronary arteries usually presented with other ST-T changes on EKG. These presentations are grouped as UA or NSTEMI, depending on whether the troponin is elevated or not. Certain anatomic characteristics of the atherosclerotic plaque make it more likely to rupture than others. These include thin fibrous cap, large lipid core populated by numerous inflammatory cells, abundant production of matrix metalloproteinase, and short of smooth muscle cells [33–37]. Plagues with these features are referred to as vulnerable plaque. Such plaques can evade angiographic detection, and may remain silent until they trigger thrombosis [38, 39]. Several factors may make plaque prone to rupture, like systemic inflammatory reactions, local shear stress, platelet hyperactivity, prothrombotic states caused by smoking, dehydration, infection, cocaine, malignancy and so on [37, 40]. Apart from the plaque rupture, vasospasm, dissection or emboli could also jeopardize the hear even in the absence of plaque [32]. In addition, invasive test like the coronaryvessels during percutaneous coronary intervention (PCI) or treatment like coronary artery bypass surgery (CABG) which may also result in myocardial necrosis.

3 Exercise and Cardiovascular System

3.1 Effects of Cardiac Disease on Exercise Performance

Exercise performance may be normal for age and sex in individuals even though they have cardiac disease [41]. However, disease that limits cardiac function may impair exercise capacity. Medications that limit the heart rate response to exercise (such as beta-adrenergic blocking agents) or restrictions in physical activity may also contribute to reduced exercise tolerance in cardiac patients.

3.2 *Effects of Exercise on Cardiovascular System*

Two main kinds of exercise have been used nowadays. They are dynamic exercise and isometric exercise. Dynamic exercise means contraction of muscles with movement at the joint [42]. Blood flow is driven towards skeletal muscle to meet the requirement for metabolism. As a consequence, blood flow is decreased in viscera (Fig. 2.1). Isometric exercise refers to sustained muscle contraction with no change in length of the involved muscle group or joint motion. Unlike dynamic exercise, isometric exercise causes a pressure load on the heart [43] (Fig. 2.2).

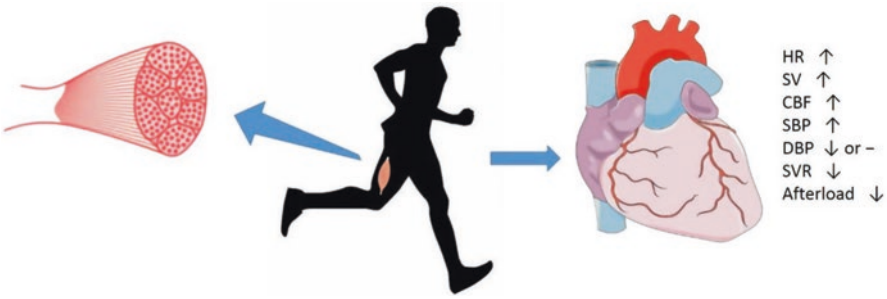

Fig. 2.1 The response of cardiovascular system to dynamic exercise. Dynamic exercise causes a range of cardiovascular responses mediated by activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system. *CBF* coronary blood flow, *DBP* diastolic blood pressure, *HR* heart rate, *SBP* systolic blood pressure, *SV* stroke volume, *SVR* systemic vascular resistance

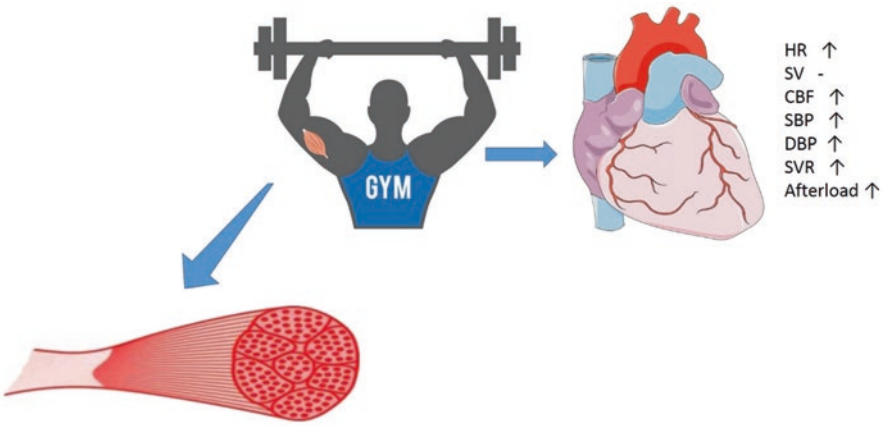

Fig. 2.2 The response of cardiovascular system to isometric exercise. Unlike dynamic exercise, isometric exercise causes no change in SVR and SV, and the increase in cardiac output is primarily driven by the increase in HR. *CBF* coronary blood flow, *DBP* diastolic blood pressure, *HR* heart rate, *SBP* systolic blood pressure, *SV* stroke volume, *SVR* systemic vascular resistance

3.2.1 Biological Effects of Exercise in the Healthy People

Biological Effects of Dynamic Exercise

Dynamic exercise can activate sympathetic nerves and inhibit parasympathetic nerves. This result in an effect of increased in heart rate(HR), systolic blood pressure (SBP), contractility, cardiac output (CO) and stroke volume(SV) [44, 45]. Among these, the increasing stroke volume and cardiac output are the secondary changes. The stroke volume is positively related to the increase in myocardial contractility [46], venous return [47] and decrease in afterload [48]. With these factors, systolic blood pressure increases during dynamic exercise [49]. However, no effect on diastolic blood pressure was observed [44].

Biological Effects of Isometric Exercise

The cardiovascular system response to dynamic and isometric exercise differs. Dynamic exercise causes functional blood congestion in the exercising muscle [50]. This local vasodilatation is limited in isometric exercise due to the sustained mechanical compression of these vessels by the muscle contraction [51]. Both systolic blood pressure and diastolic blood pressure increase in isometric exercise, so as to maintain perfusion of the contracting muscle [50, 52]. Interesting to note, the response of autonomic nervous system to isometric exercise is biphasic, with suppression of the parasympathetic nerves followed by activation of sympathetic nerve [53]. The activation of autonomic nerves stimulates increases in systolic blood pressure, cardiac output, heart rate and diastolic blood pressure. The rise in systolic blood pressure is further driven by an increase in cardiac output [54–57]. The systemic vascular resistance remains unchanged [58] or increases [59]. End diastolic volume does not change and stroke volume remains constant or decreased [60]. Therefore, the increase in cardiac output is primarily driven by an increase in heart rate [61]. With unchanged left ventricular end diastolic pressure and increased cardiac output, it is suggested that isometric exercise is able to precipitate myocardial contractility without following the Frank–Starling mechanism [56].

3.2.2 Biological Effects of Exercise in Coronary Artery Disease

Biological Effects of Dynamic Exercise

As previously discussed, dynamic exercise increases heart rate and systolic blood pressure without affecting the diastolic blood pressure [62, 63]. During dynamic exercise, the dilation of coronary arterioles, noted by a reduction in coronary vascular resistance (CVR), is required to maintain coronary blood flow (CBF) velocity [64]. It has been observed that CBF is increased in subjects with coronary artery disease [65], but not as much as in healthy subjects [46]. In patients with CAD, the

smaller residual vasodilator capacity is, the lower reserve of metabolic adaptation they have [66]. Angina symptoms prone to develop during exercise. It is because the CBF does not meet the demand [46, 67]. Underlying mechanism could be (1) dysfunctional endothelium is unable to produce endothelium-derived factors to cause adequate coronary vasodilatation [68], (2) a reduction in perfusion pressure distal to a significant coronary artery stenosis [66].

Biological Effects of Isometric Exercise

In patients with coronary artery disease, heart rate, mean arterial pressure(MAP) and cardiac output increase like in healthy individuals. However, with the unchanged systemic vascular resistance, patient with CAD less tolerate with volume load than pressure load [61]. As a result, they are at high risk of having ischemic events during isometric exercise than dynamic exercise. CBF increases with isometric exercise in CAD patients [69, 70] but the increase is smaller compared with healthy people [70]. Indeed, coronary vascular resistance decreases in healthy subjects but increases in CAD patients due to coronary vasoconstriction [71].

3.2.3 Biological Effects of Training

Biological Effects of Dynamic Exercise

Regular exercise reduces all-cause mortality, especially cardiovascular morbidity and mortality [22]. Dynamic exercise training improves cardiac adaptation to exercise. Dynamic exercise training can increase maximal cardiac output and total body oxygen consumption [46]. Exercise training can also increases basal parasympathetic nerve activity and lowers circulating catecholamine [72]. Under the effect of parasympathetic nerve system, systemic arterial resistance is decreased, which means a decrease in myocardial oxygen demand for each beat. In patients with coronary artery disease, this may translate into achievement of a higher level of exercise before their ischemic threshold is reached [73]. On the other hand, a lower heart rate reduces systolic duration relative to the duration of a normal cardiac cycle. This result in reduction in systolic compression of intramural coronary vessels and therefore decreases the net impedance to coronary blood flow [46]. Exercise training increases coronary blood flow for the same degree of myocardial work in healthy subjects through a variety of structural and functional adaptations in the coronary circulation [74]. In particular, there appears to be a beneficial effect on arterial endothelial function including attenuation of acetylcholine-driven vasoconstriction, increased nitric oxide production and elevated sensitization of the microvasculature to adenosine-mediated vasodilatation [75]. Furthermore, while training in subjects with CAD has been shown to increase collateral vessel growth, no such phenomenon has been observed in healthy subjects [46].

Biological Effects of Isometric Exercise Training

Isometric exercise training does not increase volume load and the cardiovascular adaptations are different to those seen with dynamic exercise [43]. Also, isometric training does little to improve aerobic capacity or cardiovascular efficiency [76], and no significant sustained changes in stroke volume nor cardiac output have been observed [77, 78]. However, isometric training does lower resting blood pressure. Although the mechanism is unclear [79]. It is hypothesized that sympathetic nervous system, systemic vascular resistance and oxidative stress may be involved [80].

4 Exercise and Acute Coronary Syndrome

4.1 General Concept

It is crucial to clarify the difference of physical activity and exercise training. Physical activity and exercise training have different concepts and body movement. Moreover, these tools are applied in different contexts, depending on the purpose chosen by the healthcare team (e.g., physical educator, physiotherapists, nurse, physician). The American College of Sports Medicine (ACSM) has defined physical activity as any body movement performed in response to voluntary muscle contraction that increases energy expenditure [81]. Thus, it is important to understand that winking or shaking are not considered physical activity, even if they are types of body movement. Walking in the park or talking with a friend is considered as physical activity. Because the contraction of leg muscles is voluntary and the energy expenditure increases exponentially from baseline levels. While exercise training means a planned and structured body movement aimed to improve one or more physical capacities. Exercise training has different designs, and can be introduced as, for example, aerobic and strength/resistance exercise, swimming training, yoga, among others, depending on the approach.

The American Heart Association (AHA) describes physical activity as an important treatment tool. Physical activity can be applied to treat a variety of diseases as hypertension, diabetes mellitus type II, obesity. Physical inactivity is strongly associated with coronary artery disease risk factors, morbidity and mortality [82]. What's more, AHA strongly encourages the inclusion of physical activity in the lifestyle changes of patients who aim to decrease coronary artery disease risk [82]. General recommendations recommend that adults should achieve, at least, 150 min of moderate-intensity activity or 75 min of vigorous-intensity activity per week to prevent coronary artery disease [82, 83].

Exercise training is more often used in cardiac rehabilitation for secondary prevention. The effectiveness of exercise training depends on lots of factors like volume, intensity, endurance time, individual difference, etc., and all these factors are

difficult to control in observational studies. Because of this, the epidemiological data is still lacking. However, the effects of exercise training on coronary artery disease risk factors are widely elucidated in clinical trials, experimental studies and observational studies (i.e., cross-sectional). Exercise training has been demonstrated to improve exercise tolerance, quality of life, functional capacities and job-related physical tasks, as well as decrease cardiovascular risk factors and cardiac mortality [84]. For now, it become a consensus that exercise training should compose the rehabilitation programs of cardiac patients.

4.2 Exercise in Angina Pectoris

The mainstay treatment of angina pectoris is medication, percutaneous transluminal coronary angioplasty (PCI) or coronary artery bypass grafting (CABG). With rare exceptions, much of the evidence that exercise training enhances effort tolerance in patients with angina pectoris could be obtained [85]. Exercise training eliminates angina symptoms by at least two mechanisms. First, it increases VO_2max, thereby reducing the heart rate and systolic blood pressure in response to submaximal exercise. Second, exercise training improves endothelial function [86]. Normal functioning endothelial system is crucial for compensating blood flow in response to stress. During exercise, normal coronary arteries is able to dilate, whereas atherosclerotic coronary arteries often fail to do so because of endothelial dysfunction [86].

Physical activity is negatively associated with the severity of disease. A total of 2172 patients with ACS were enrolled into the study (1649 men and 523 women). Among them, 764 patients (35%) were diagnosed as having unstable angina pectoris. This study proved that physical activity was associated with a reduction of in-hospital mortality. It appears that an active lifestyle may confer protection during the first month after the attack, in terms of both mortality and re-hospitalization due to a recurrent event. Also, this study found out that instead of CK-MB level, troponin I was highly related to physical activity status [87, 88].

Other studies revealed a revised endothelial activity after exercise training [21, 89, 90]. Previously, exercise training is commonly applied in patients with angina who are not candidate for coronary interventions. Results of a clinical trial opposed this. A total of 101 men 70 years old or younger were randomly assigned to 1 year of exercise training or to percutaneous transluminal coronary angioplasty (PTCA). Patients in exercise training group underwent 6 daily 10-min sessions performed at 70% maximal heart rate, followed by daily 20-min home bicycle sessions plus a weekly 60-min supervised session. The exercise level at the onset of ischemia increased 30% in the exercise trained subjects and 20% in the PTCA subjects. Although differences were not significant, but the increase in maximal exercise capacity (20% vs. 0%) and VO_2max (16% vs. 2%) were significantly greater in the exercise-trained subjects. At 1 year follow up, 88% of the PCI subjects versus only 70% of the exercise-trained subjects experienced major cardiovascular events

including myocardial infarction, stroke, revascularization procedure, or hospitalization for angina ($P = 0.023$) [85].

4.3 Exercise in Myocardial Infarction

It was demonstrated that adherence to exercise at 30 days after acute coronary syndrome is associated with a substantially lower rate of short-term major cardiovascular events and all-cause mortality [91]. This study included 18,809 patients from 41 countries enrolled in five randomized clinical trial of the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS). Adherers to diet and exercise had a 50% lower risk for all major events in 6 months compared with no adherers. The risk associated with diet alone or exercise alone was similar for myocardial infarction and stroke, but for death, exercise may have more significant effect. Diet and exercise adherence was associated with a decreased risk of myocardial infarction compared with no adherence.

Promotion of collateral growth is one of the effective therapeutic strategies in patients with myocardial infarction. Physical exercise plays a fundamental role in arteriogenesis. It increase cardiac output, elevates the coronary flow along the arterial branches, thus improves collateral function [92, 93].

A phenomenon that attenuation of myocardial ischemia with an associated increase in ischemic threshold in patients with repeated ischemic episodes was observed in the 1990s. This has later was recognized as ischemic preconditioning (IPC). Induced by repeated bouts of exercise, IPC has been shown to induce a decrease in mean maximal ST depression and ischemia duration on subsequent exercise [94].

Interesting to note, traditional cardiovascular biomarkers (cTnT, hs-cTnT, BNP, NT-proBNP, and d-dimer) and echocardiogram are prone to alterations due to strenuous exercise. In this circumstance, it is important to take previous physical exercise into consideration when ACS is suspected [95].

4.4 Exercise-Based Cardiac Rehabilitation

4.4.1 Historical Perspective

Cardiac rehabilitation generates secondary prevention of CAD and is an essential component of care for all cardiac patients [96, 97]. It consists of medical, physical, social and psychological intervention. It favorably influences the underlying risk factors in order to stabilize, slow and even reverse disease progression. Therefore cardiac rehabilitation facilitates the ability of the patient to preserve or resume an active and functional contribution to the community [98, 99]. Cardiac rehabilitation promotes quality of life through increasing cardiac function and exercise tolerance,

improving cardiovascular symptoms, reducing levels of anxiety, depression and stress, and maintaining independence in activities of daily living [97, 99, 100].

Shorter hospitalizations, along with effective medications and procedures have changed cardiac rehabilitation program. Nowadays, exercise training, physical well-being counseling, medication compliance and diet are key components of the rehabilitation [82]. U.S. Centers for Medicare & Medicaid Services (CMS) guidelines reflect these changes and stipulate that "cardiac rehabilitation programs must be comprehensive and…include a medical evaluation, a program to modify cardiac risk factors…prescribed exercise, education, and counseling." Consequently, cardiac rehabilitation programs are now often referred to as "cardiac rehabilitation/secondary prevention programs". The American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) recommend comprehensive cardiac rehabilitation programs for patients who have undergone percutaneous transluminal coronary angioplasty (PTCA), CABG, post ACS, stable angina or peripheral vascular disease [101]. This recommendation has the highest level of evidence (level A) for all conditions except angina (level B) [101]. The Centers for Medicare & Medicaid Services also defines comprehensive cardiac rehabilitation "reasonable and necessary" for patients after valve surgery and heart or heart and lung transplantation [102]. They proposed using referral to cardiac rehabilitation as a core performance measurement for the management of patients with coronary disease and after cardiac surgery starting in January 2014, with an impact on hospital reimbursement in 2015 [103]. Consequently, interest in cardiac rehabilitation will increase in the near future [104].

Structured exercise has been identified as being central to the success of cardiac rehabilitation [105–107]. Back in the early 1950s, exercise was not advised in MI patient. In contrast to traditional concepts, increasing evidence has shown that exercise have beneficial effects on cardiovascular system. Exercised-based cardiac rehabilitation has gradually come into view and has developed to reverse the restriction of physical activity. Exercise training is central to most cardiac rehabilitation/risk reduction programs because it increases exercise capacity and reduces exercise-induced angina. In addition, exercise training is one of the few prevention techniques that reduce angina in the time before beta-adrenergic blocking agents and coronary artery revascularization procedures [21]. Nevertheless, some studies argues against the protective effect of exercise training. A meta-analysis including 21,295 patients with CAD noted the reductions in mortality and recurrent myocardial infarction were similar for programs that involved exercise and programs that do not [28].

4.4.2 Effect of Exercised-Based Cardiac Rehabilitation on Patients with Acute Coronary Syndrome

Exercise-based cardiac rehab improves mortality and decrease readmission after ACS. A total of 10,794 patients with myocardial infarction, CABG, PTCA and angina were randomly assigned to exercise-based cardiac rehabilitation or usual

care. At 12 month follow-up, total mortality and cardiovascular mortality were 13% and 26% lower respectively compared to usual care group. Meanwhile, hospital admissions were 31% lower in the first year of the study ($P < 0.05$ for all). Subsequent MI, CABG, or PTCA did not change [106]. A variety of secondary prevention programs, including those without an exercise component, can obtain similar results [98].

Aerobic endurance training is fundamental for exercise-centered rehab program [108]. It improves cardiorespiratory fitness and functional capacity, reduces disease-related symptoms and favorably influences coronary risk factors [109, 110].

PTCA has been recognized as the most effective treatment for ACS [111, 112]. A retrospective analysis of 2395 patients after PTCA noted an approximately 45% reduction in mortality ($P < 0.001$) in the 40% of patients who participated in exercised-based cardiac rehabilitation. What's more, the reduction in mortality did not differ by sex, age, or PTCA urgency. Therefore, this suggests that cardiac rehabilitation can benefit almost all patients after PTCA [107]. Although selection bias cannot be ruled out, the overwhelming beneficial effect from cardiac rehab remains promising (Table 2.1).

5 Conclusion

It has been established that exercise was crucial for both prevention and recovery in patients with CAD [113–120]. Recent studies have shed light on the mechanisms that may responsible for cardiac alterations after ACS and the beneficial adaptations promoted by exercise [121–125]. In spite that majority of studies have proved the protective effect of exercise ACS, problems still exist in interpretation. Regarding the effect of prevention, exercise have the potential to act by pre-conditioning the heart to ischemic [126–128]. IPC has been found to exert its protective effect in a two phase manner [129–131]: the classic or early pre-conditioning that lasts for about 3 h after the exercise bout, and the late pre-conditioning, or "second window of protection," which begins approximately a day later, and may last up to 72 h. The underlying explanation to this could be increased expression and synthesis of cyto-protective factors. It is not easy to detect the cardio protective effect of the short-lived early IPC in clinical application [130] since there is no way to predict the occurrence of ACS yet. The second window may at least in part explain the reduced severity of myocardial damage during ACS, as evidenced in the physically active subjects in the study [130, 132]. It is not known yet whether the cardio protective effects of physical activity status may have more lasting effects to favourably impact short-term prognosis during recovery from an acute coronary syndrome [133]. Alternatively, the reduced severity of myocardial necrosis observed in the physically active individuals may be the main factor for a better prognosis at the recovery period [134]. Based on this, it is reasonable to assume that revascularization therapies may be more effective in a less damaged myocardium [135, 136], such as in the case of physically active individuals [137].

Table 2.1 Benefits of exercise in acute coronary syndrome

Benefits	Change
Improvement in exercise capacity	
Estimated metabolic equivalents	↑
Peak oxygen consumption	↑
Peak anaerobic threshold	↑
Improvement in lipid profiles	
Total cholesterol	↓
Triglycerides	↓
HDL-C	↑(higher in patients with low baseline)
LDL-C	↓
LDL-C/HDL-C	↓(higher in certain subgroups)
Reduction in inflammation	
hs-CRP	↓
Reduction in indices of obesity	
BMI	↓
Fat	↓
Metabolic syndrome	↓
Improvements in behavioural characteristics	
Depression	
Anxiety	
Hostility	
Somatization	
Overall psychological distress	
Reduction in stress-related increased mortality	
Improvements in quality of life and components	
Improvement in autonomic tone	
Increased heart rate recovery	
Increased heart rate variability	
Reduced resting pulse	
Improvements in blood rheology	
Improvements in social benefits	
Reduction in hospitalization costs	
Reduction in major morbidity and mortality	

BMI body mass index, *hs-CRP* high-sensitive C-reactive protein, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoproteincholesterol

As for the effect of treatment and recovery, The major problem with exercise-based cardiac rehabilitation currently is its underutilization [138, 139]. Only 14–35% of MI survivors and approximately 31% of patients after PCI were referred to cardiac rehabilitation programs [140]. Women, elderly, and minorities—the very groups at greatest risk for recurrent events—have especially low referral rates [141,

142]. Physician endorsement of cardiac rehabilitation is one of the most important predictors of participation. The possible causes of the low referral rates could be: (1) underestimating the benefit of exercise; (2) health professionals' lack of knowledge on exercise training; (3) absence of exercise training propagation; (4) lack of a conclusive clinical trial [143–147]. Besides, in some circumstances, individual compliance contribute a lot to the successful of rehab. Physician referral will probably increase when such action becomes a core measure of hospital performance. Including an automatic referral to cardiac rehabilitation in standardized order sets for qualified patients is among the best ways to solve the problem [148, 149]. On the other hand, if Medicare adopts the referral to exercise-based rehab as one of the performances measurement for patient's management, not only the referral rate would be increased, but also the medical care costs would be controlled [150]. Although current data supporting the benefits of exercise-based treatment are highly regarded, standard-powered clinical trial remains insufficient. Most of the evidence were provide by meta-analysis, of which publication bias is inevitable. Also, many of the trials evaluated in the available meta-analyses included studies that predate the present aggressive medical and interventional therapy [151], thus make the conclusion more obscure. Because of this, payers may reluctant to reimburse exercise-based treatment, even though this outcome seems unlikely given Medicare's present evaluation of these data [152]. As the other way around, since the cost of the interventional procedure is huge, cost-effective management like exercise-based treatment and risk reduction programs may be applied before proceeding to pricy ones. Such a change seems impossible in the present fee-for-service model. Given the available comparison of medical versus invasive strategies, it is still realistic [153–156].

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