1. Basics of Cardiac Rehabilitation

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1.1 Definition

According to the World Health Organization definition, cardiac rehabilitation is "the sum of activities required to influence, favorably, the underlying cause of the disease, as well as to provide the best possible physical, mental, and social conditions, so that patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behavior, slow or reverse the progression of a disease" [1,2]. The objectives of exercise-based cardiac rehabilitation are to increase functional capacity level, reduce anginal symptoms and disability, improve quality of life, modify coronary risk factors, and reduce morbidity and mortality rates [3].

Key elements of the comprehensive cardiac rehabilitation program include [3,4]:

- Clinical assessment;
- Optimal pharmacotherapy;
- Optimal function of implanted electrical cardiac devices;
- Individually tailored exercise prescription;
- Nutritional counseling;
- Weight control management;
- Lipid management;
- Blood pressure monitoring;
- Smoking cessation;
- Psychosocial support;
- Education of the patients and their relatives;
- Monitoring of the effects of cardiac rehabilitation.

Exercise prescription remains a core component of cardiac rehabilitation.

A significant reduction in cardiovascular mortality and hospitalization has recently been validated by Cochrane analysis. The beneficial effects of cardiac rehabilitation reported in a group of patients after myocardial infarction include reductions in [5–7]:

- All-cause mortality by 11–26%;
- Cardiac mortality by 26–36%;
- Unplanned admissions to a hospital by 28–56%.

More recent Cochrane review demonstrated a significant reduction in cardiovascular mortality in exercising group compared with controls (10.4% and 7.6% respectively) [8].

The specific mechanisms responsible for these beneficial effects remain disputable, especially considering the insignificant reduction in the recurrence of myocardial infarction after cardiac rehabilitation. It has been postulated that mortality reduction is a result of a reduction in ventricular fibrillation (decreased sympathetic tone and enhanced parasympathetic tone) or due to the mechanism of ischemic preconditioning [9]. As cardiorespiratory fitness improvement is associated with reductions in mortality after a structured, comprehensive cardiac rehabilitation program, the exact mean change in fitness that occurs has been extensively studied. Sandercock's review of 31 studies demonstrated an increase in fitness of 1.55 metabolic equivalents after phase II. Converting this value to peak oxygen uptake, a gain in cardiorespiratory fitness of 5.4 mL/kg/min can be expected. The reported extent of gain was strictly related to the number of sessions completed, with >36 exercise sessions resulting in a greater gain in fitness [10]. As expected, programs with a significantly lower number of sessions resulted in a smaller increase in cardiorespiratory fitness [11].

The effectiveness of cardiac rehabilitation in reducing either cardiovascular mortality or the rate of myocardial re-infarction largely depends on the exercise volume. Data from meta-analyses have demonstrated specific requirements for the best cardiac rehabilitation outcomes as presented in Table 1 [12].

Table 1. Optimal conditions for efficacious cardiac rehabilitation.

Intervention	Multicomponent program
Start	Commenced within 3 months after discharge.
Settings	Inpatient/outpatient/community or home-based/hybrid telerehabilitation).
Exercise components	Frequency: at least two supervised sessions/week Duration: at least 36 sessions.
Other components	Management of: smoking cessation, physical exercise training, counseling for exercise/activity, diet, blood pressure, cholesterol, glucose levels, checking medication, stress management.

Source: Authors compilation based on data from [12].

1.2. Development

In the 18th century, Heberden reported that exertion reduced the frequency of anginal pain. He described a patient's health improvement after sawing wood for 30 min every day [13]. The practice of imposing limited mobility on patients

with acute coronary events, however, continued over the next 150 years, leading to prolonged hospital stays and declines in functional capacity [14]. In the 1930s, patients remained bedridden for 6 weeks following myocardial infarction due to the pathologic finding that the infarction evolution process from initial ischemic necrosis to the formation of a stable scar lasts over 6 weeks. Chair therapy was introduced in the 1940s, and, from the early 1950s, a strategy of very short daily walks lasting five minutes was advocated, but only after a coronary event and four subsequent weeks of rest [15]. In 1968, a study by Saltin demonstrated the importance of exercise and the detrimental effect of prolonged bed rest [16]. Further studies by Braunwald, Hutter, Askanas, Rudnicki, Boyle, Sonnenblick, Hellerstein, Naughton, and many others established a strong case for the benefits of exercise and supported the use of early mobilization in hospital settings [17]. As a result, a phasic, multi-profile model of cardiac rehabilitation has gradually been implemented, including a return to work and social activities [18]. Early ambulation has become standard and evolved into phase 1 or inpatient cardiac rehabilitation. Activities performed in the coronary intensive care unit are typically limited to 2 METs and include self-care (such as bed bathing, sitting in a chair) and passive and active ranges of motion. The further rapid development of the use of interventional techniques in cardiology, however, has significantly shortened the duration of hospitalization following an acute coronary event to 3–5 days, thus allowing for more intense mobilization processes to be used.

Contemporary cardiac rehabilitation has gradually evolved into a comprehensive secondary prevention, multi-factorial program consisting of exercise training; the management of cardiovascular risk factors; and nutritional, psychological, behavioral, and social support to improve patient outcomes. The target population for cardiac rehabilitation has expanded significantly over the years, but post-myocardial infarction survivors remain a key population. In the guidelines of the European Society of Cardiology and the American Heart Association, cardiac rehabilitation is mandatory—i.e., it has class I recommendations for therapeutic intervention in many cardiac conditions (e.g., acute coronary syndromes, percutaneous coronary interventions and/or myocardial revascularization surgery, stable coronary artery disease, heart failure, cardiac transplant, left ventricular assistance devices or other implanted devices (cardiac pacemakers, cardioverter-defibrillators, cardiac resynchronization devices), cardiac surgery, and high cardiovascular risk-factor profiles) [19]. The different classes of recommendations, with the corresponding level of evidence-based indications needed for the most frequently referred groups of patients, are listed in Table 2.

Table 2. Evidence-based indications for cardiac rehabilitation.

Target Group	Class of Recommendations	Level of Evidence
Acute coronary syndromes	I	A
Surgical revascularization	I	B
Chronic coronary syndromes	I	B
Heart failure with reduced or preserved ejection fraction	I	A

Source: Table by authors.

Cardiac rehabilitation is constantly evolving, with new ideas and strategies being implemented all the time. Examples of new strategies are, hybrid telerehabilitation and high-intensity interval training. Recent COVID 19 pandemic highlighted the role of cardiac telerehabilitation as an efficacious, safe, and essential part of cardiac rehabilitation. There is still, however, a need to enhance cardiac rehabilitation enrollment due to the lower cardiac rehabilitation referral and participation rates of women, the elderly, and minorities [20–22]. Furthermore, cardiac rehabilitation is offered in just 55% of countries, as exhibited in Figure 1 [23].

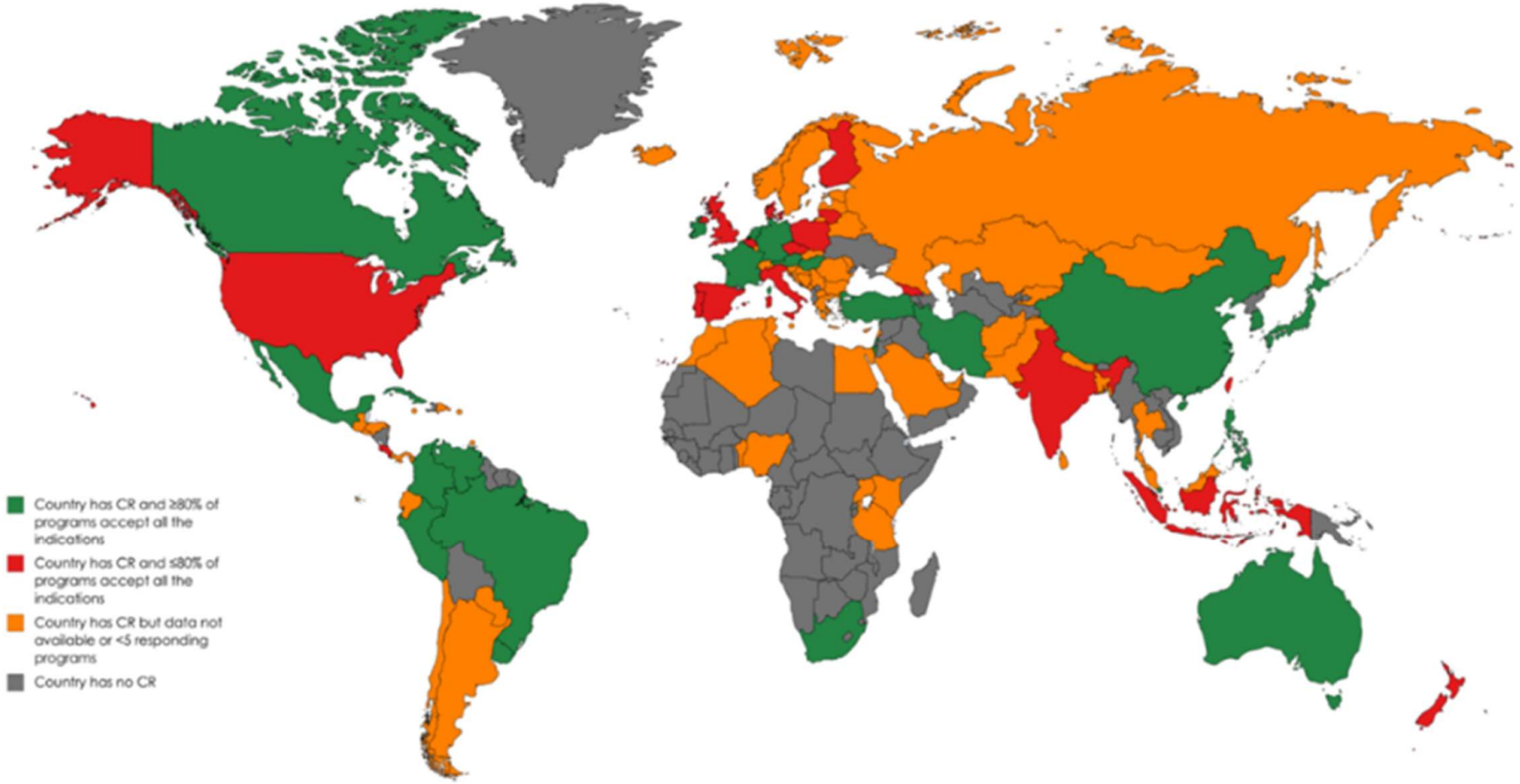

Figure 1. Global cardiac rehabilitation availability. Source: Reprinted from [23].

Thus, the distribution of cardiac rehabilitation services to the highest possible number of eligible patients should be prioritized, as should overcoming many existing barriers—e.g., the insufficient education of patients, poor adherence, lack of availability of structured programs, etc.

1.3 Phases

Cardiac rehabilitation typically comprises three phases [4]:

- Early cardiac rehabilitation:
    - Phase I: in-patient (typically 4–14 days).
    - Phase II: multidisciplinary supervised structured program (4–12 weeks).
- Late cardiac rehabilitation:
    - Phase III: home- or community-based maintenance phase (lifelong).

Phase I:

Phase I, or the inpatient phase, typically begins at the coronary care unit, intensive care unit, postoperative ward, or cardiac rehabilitation ward. It should begin as soon as the patient stabilizes after an acute cardiac event and should be continued until their discharge from hospital. Phase I comprises:

- Early patient mobilization by a physiotherapist in cooperation with a supervising physician (usually an intensive care unit physician). Mobilization rate is based mainly on the patient's clinical status and adaptation to mobilization and should aim to help them to achieve the level of activity required to leave hospital.
- Prevention of complications secondary to immobilization.
- Identification of personal cardiovascular risk factors.
- Individual plan to support lifestyle changes.
- Short-term education in the form of individual talks and the delivery of dedicated leaflets with information regarding cardiac events, psychological responses to these events, and the management of cardiac symptoms.
- Psychological screening assessment in the form of questionnaires.
- Discharge home activities plan, including walking, lifting weights, returning to work, and resumption of sexual activity.
- Referral for phase II.

Phase I B (provided in some countries):

The transitional phase encompasses the period from hospital discharge until the start of the structured program and includes:

- Education in the form of home visits or phone calls by a cardiac rehabilitation team member, usually a nurse.

- Control of gradual low-level home activity program progression.

Phase II:

Phase II should start as soon as possible, preferably within two weeks of discharge.

Phase II can take the form of a structured, multidisciplinary, supervised outpatient, residential, or hybrid program and usually lasts up to 12 weeks. Prior to the commencement of a medically supervised exercise training program, an initial assessment and risk stratification will be performed by a cardiologist. Risk stratification is based on the severity of symptoms, left ventricular function, functional capacity level, and the presence of residual ischemia or arrhythmia [24]. Phase II also includes comprehensive education and counseling regarding modifiable cardiovascular risk factors, the optimization of medical therapy, smoking cessation programs (if necessary), vocational counseling, and stress management. Residential phase II programs, typically lasting 3–4 weeks, should be limited to:

- High-risk patients;
- Patients with clinical instability;
- Patients with complications related to acute events or procedures;
- Patients with serious comorbidities;
- Frail patients;
- Patients with advanced heart failure (NYHA classes III and IV);
- Patients who underwent heart transplantation or the implantation of a left ventricular assistance device;
- Those who cannot attend outpatient programs for reasons such as them being a very long distance from the patient's home.

At the end of phase II, a re-assessment should be performed (focusing on clinical status, functional capacity, quality of life, psychological and nutritional status), and the patient's progress should be documented [12].

Phase III:

Phase III rehabilitation should be offered as a long-term (lifelong) maintenance phase to patients after they have completed phase II. It can take place in a cardiac rehabilitation or community-based center or be implemented as a home exercise program. Hybrid cardiac rehabilitation with remote monitoring is available in some countries [25]. A follow-up assessment of patients who have completed the phase II program by a cardiac specialist is essential.

1.4 Indications

Cardiac rehabilitation has evolved over the decades from simple monitoring after myocardial infarction into a comprehensive, multidisciplinary approach.

Similarly, its indications have been expanded and now encompass patients with many cardiovascular diseases. As the organization and delivery of cardiac rehabilitation programs in different countries depend on local policies, traditions, and resources, the indications for cardiac rehabilitation can vary between countries [24].

Indications for cardiac rehabilitation include [2,4]:

- Ischemic heart disease:
    - Acute coronary syndromes;
    - PCI and/or myocardial revascularization surgery;
    - Stable coronary artery disease with multiple risk factors.
- Stable heart failure.
- Cardiac surgery:
    - Coronary artery bypass graft surgery;
    - Valvular surgery;
    - Heart transplant.
- Percutaneous valvular prosthesis or MitraClip.
- Implantation of electrical cardiac devices: pacemaker, cardioverter-defibrillator, or cardiac resynchronization therapy.
- Implantation of a left ventricular assistance device.
- Peripheral arterial disease.
- Pulmonary hypertension.
- Following aorta surgery procedures

Other indications include:

- Patients with ischemic heart disease awaiting surgery;
- Patients with cardiomyopathies;
- Patients with congenital and acquired heart diseases;
- Patients who had major vascular surgery;
- Patients after myocarditis (post-acute phase);
- Patients with dysrhythmias;
- Individuals with cardiovascular risk factors—i.e., with diagnoses of diabetes, dyslipidemia, arterial hypertension [26].

1.5 Contraindications

Most patients referred for cardiac rehabilitation are eligible to participate in the program. The early assessment of these patients, including physical evaluation and risk stratification, before they commence exercise sessions should be carried out to ensure safety [24]. Contraindications for exercise training are generally accepted to include [2,4]:

Absolute contraindications:

- Recent acute coronary syndromes (within a few days);

- Resting ECG changes suggesting significant ischemia;
- Presence of ischemia < 3 METS or <50 watts;
- Uncontrolled dysrhythmias;
- Decompensated heart failure;
- Severe aortic stenosis or severe grade of another valve disease;
- Acute myocarditis or/and pericarditis;
- Aortic dissection;
- Acute pulmonary embolism;
- Acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise—e.g., infection or thyrotoxicosis;
- Acute thrombophlebitis;
- Hypertrophic cardiomyopathy with left ventricular outflow tract stenosis;
- Physical disability that would affect safe and adequate exercise performance.

Relative contraindications:

- Electrolyte abnormalities;
- Tachyarrhythmia or bradyarrhythmia;
- A high-degree atrioventricular block without a pacemaker;
- Atrial fibrillation with uncontrolled ventricular rate;
- Hypertrophic cardiomyopathy without left ventricular outflow tract stenosis;
- Resting systolic blood pressure > 180 mmHg;
- Resting diastolic blood pressure > 110 mmHg;
- Mental impairment leading to an inability to cooperate during exercise training;
- Orthostatic hypotension > 20 mmHg, with symptoms;
- Uncontrolled diabetes mellitus, with a glucose level >300 mg/dL.

1.6 Cardiovascular System and Exercise

The interplay between the cardiovascular system and exercise basically depends on the type of exercise (aerobic, resistance) performed, the exercise intensity and duration, and muscle mass involvement [27]. The most striking neurohormonal response to regular physical activity is improved cardiac parasympathetic regulation. It has been demonstrated that the heart rate values of very well-trained individuals can reach as low as 30–35 beats per minute [28].

Regular high-intensity exercise training may result in cardiac morphological adaptation, called athlete's heart—i.e., myocardial hypertrophy, which is more eccentric in patients who perform endurance training and more concentric in patients who perform resistance training [29]. It has been demonstrated that the mean left ventricular end-diastolic diameter in athletes increases compared with that in normal subjects, with typical values equal to 53.7 mm and 49.6 mm, respectively [30]. Morphological changes in the left ventricle after regular exercise have also been validated in patients with chronic heart failure. Hambrecht demonstrated reverse left ventricular remodeling with the slight improvement of the left ventricular ejection

fraction from 30% to 35% after aerobic training in patients with ischemic and dilated cardiomyopathy. It has been postulated that reverse remodeling is evoked by the peripheral effects of aerobic training—i.e., improved antioxidative protection in the skeletal muscle, enhanced parasympathetic tone, and improved vasodilation [31]. To date, aerobic training has also been found to improve left ventricular diastolic filling at rest and during exercise [32]. Increases in the cross-sectional area of the coronary arteries and in coronary collateral formation have been demonstrated in animal models due to the use of a regular training program [33]. A growing body of evidence indicates that regular endurance exercise reduces the risk of death during clinical ischemia-reperfusion injury due to it offering enhanced antioxidative protection [34]. Another postulated cardioprotective effect of regular exercise is the improved electrical stability of the heart, which has been demonstrated in animal models [35,36].

Hemodynamic adaptations to exercise include increases in stroke volume. The resting stroke volume of individuals who exercise regularly may reach 100 mL due to prolonged diastolic filling period. During submaximal exercises, stroke volume increases by 20–40 mL and may reach as high as 160 mL during maximal exertion [37]. The impacts of aerobic and resistance exercise on blood pressure have been the subject of debate in the past due to safety concerns. Exercise has been shown to reduce blood pressure in both normotensive and hypertensive individuals [38]. The beneficial effect of regular exercise on plasma glucose and triglycerides has been well established [39–45]. Table 3 shows the main effects of regular exercise on the cardiovascular, neurohumoral, and other systems.

Table 3. Effects of regular exercise.

Type of System	Type of Effect
Cardiac	Ischemia-reperfusion protection; Physiologic hypertrophy; Reverse left ventricular remodeling; Electrical stability; Improved left ventricular relaxation.
Vascular	Reduced stiffness of aorta; Increased vasodilation.
Others	Neurohumoral: increased parasympathetic tone and reduced sympathetic response; Respiratory: increased vital capacity; Rheological: reduced coagulability.

Source: Table by authors.

1.7. Exercise-Induced Preconditioning

1.7.1. Ischemia-Reperfusion Injury (IRI)

Definition

Acute myocardial infarction (AMI) is the leading cause of morbidity and mortality worldwide [46]. Reperfusion procedures that involve restoring the blood flow to the ischemic region as quickly as possible are the chief therapeutic goal of AMI [47]. The primary pathological cause of AMI is paradoxical cardiomyocyte dysfunction, known as ischemia-reperfusion injury (IRI) [48]. Ischemia-reperfusion injury (IRI) is defined as the paradoxical exacerbation of cellular dysfunction and death following the restoration of blood flow to previously ischemic tissues [49].

Severity Levels of IR-Induced Cardiac Injury

The three different severity levels of IR-induced cardiac injury are proportional to the duration of ischemia. The lowest level of injury is cardiac arrhythmias followed by rapid reperfusion after one to five minutes of ischemia without impaired myocardial contractile performance or cardiac cell death. The second level of injury is five to 20 min of ischemia-reperfusion, termed as myocardial stunning, characterized by ventricular contraction deficits that last 24–72 h following the insult without cardiac cell death. The third and most severe IR injury level is myocardial cell death, which occurs when the duration of ischemia exceeds 20 min. During this IR injury level, cardiac myocytes are irreversibly damaged, and death occurs due to apoptosis and necrosis processes that take place within ventricular myocytes [48].

1.7.2. Ischemic Preconditioning

Definition

Ischemic preconditioning refers to the protection of the ischemic myocardium by short periods of sublethal ischemia separated by short bursts of reperfusion delivered before the ischemic insult [50]. It provides the myocardium with a powerful means of protection against acute myocardial ischemia and makes it more resistant to a subsequent ischemic insult. In addition, reconditioning protects against postischemic contractile dysfunction and ischemia- and reperfusion-induced ventricular arrhythmias. Ischemic preconditioning has two phases of protection. The early phase develops within minutes of the initial ischemic insult and lasts 2 to 3 h. The late phase becomes apparent 12 to 24 h later and lasts 3 to 4 days [51].

Experimental Models

Ischemic preconditioning has been demonstrated in several animal species, as well as in isolated human cardiomyocytes [50]. This term was introduced in 1986 by Murry et al., who investigated this phenomenon on an open-chest canine. An experimental dog group was exposed to four consecutive periods of ischemic episodes (5 min coronary occlusions interspersed with 5 min reperfusion periods) then subjected to a prolonged, more severe ischemic insult (a 40 min coronary occlusion followed by four days of reperfusion). The control dogs group underwent the 40 min occlusion with no prior exposure to ischemia. Surprisingly, the experimental dogs showed markedly reduced infarct size (75%) compared to the controls, and this effect was independent of differences in coronary collateral blood flow [52].

Remote Ischemic Conditioning (RIC)

It has been well established that preconditioning protection does not require brief ischemia to be applied directly to the myocardium itself. Remote ischemic conditioning was originally observed as a laboratory curiosity in non-invasive cardioprotective therapy, wherein brief bouts of ischemia-reperfusion in one coronary vascular region reduced the infarct size resulting from the sustained occlusion and reperfusion of an adjacent coronary artery. Moreover, studies have shown that RIC is a systemic phenomenon and can be evoked from longer distances [53]. For example, local insult induced by ischemia-reperfusion in the extremities or other parenchymal organs can elicit protection in the heart (in which the infarct size is reduced).

RIC can be achieved by inflating a standard sphygmomanometer cuff placed on the upper arm above systolic pressure to restrict blood flow temporarily by utilizing four cycles of five minutes of cuff inflation interspersed by five minutes of complete cuff deflation. More recently, an automated RIC device was created with the intention of providing RIC to adult patients undergoing cardiothoracic surgery or procedures [54]. In addition, RIC is an essential mechanical intervention to induce cardio protection accompanying reperfusion in patients with AMI because this method is non-invasive and can be applied during coronary occlusion before primary PCI.

1.7.3. Exercise Promotes Preconditioning

It has been well established that exercise and elevated physical activity have beneficial effects in reducing CVD risk and providing protection from cardiovascular events. Exercise displays a strong correlation with decreased risk of myocardial infarction (MI) and limits the damage caused by ischemia and reperfusion if such an MI event occurs [48]. Like the ischemic preconditioning phenomenon, the

protection provided by exercise appears to occur in a biphasic manner, with two separate phases of protection, beginning immediately after a single episode of exertion and continuing for multiple days. The first phase begins immediately following the acute exercise bout and quickly subsides within three hours of preconditioning. Then, after approximately 24 h, the second phase of protection begins, persisting for at least nine days and potentially extending to several weeks. This phase has been reported to be more robust than the first phase [55]. The mechanisms contributing to exercise-induced preconditioning include the activation of mitochondrial antioxidant enzyme superoxide dismutase (SOD2) in ventricular myocytes and the increased expression of mitochondrial potassium channels [48]. The mechanisms and underlying causes of the warm-up phenomenon were investigated by Tomal et al. in 1996 [50]. In this study, patients with coronary artery disease underwent two consecutive exercise tests (ET), followed by a third test two hours later. The rate–pressure product before the onset of ischemia decreased during the third ET ($p < 0.005$) by more than during the first and second ET. In addition, the time to both 1–5 mm ST-segment depression and anginal pain onset was higher during the second and third ET ($p < 0.001$, respectively). Thus, this study suggested that the warm-up angina phenomenon observed within minutes of a first ET results from adaptation to ischemia through improvements to myocardial perfusion or preconditioning, increasing both the time to ischemia and the ischemic threshold. In contrast, the warm-up angina phenomenon observed two hours after repeated ET results from a slower increase in cardiac workload, causing an increase in time to ischemia but not in the ischemic threshold.

Training below the level of the ischemia threshold will not place sufficient ischemic stress on the myocardium to induce exercise IPC. One study compared the effects of an 8-week interval training program carried out in two groups of patients with stable angina by assessing the influence of warm-up ischemia prior to training conducted either at or below the ischemic threshold. One group underwent pre-training exercise IPC and the other group did not. The exercise IPC group showed a statistically significant improvement in all post-training variables except for maximum ST depression (STD). The improved variables included maximal workload (28%), walking distance (24%), exercise duration (20%), and time to 1 mm STD (28%). Moreover, the beneficial effect of training in the exercise IPC group on both exercise-induced ischemia and physical capacity was sustained for up to 10 days and 1 month, respectively [56]. Thus, based on the results of Korzeniowska-Kubacka et al., the warm-up effect of exercise IPC may have a major beneficial effect and appears to be necessary for exercise training in cardiac rehabilitation. Thus, cardioprotective strategies that have been used in clinical studies for acute myocardial infarction entail early and late ischemic preconditioning evoked by brief episodes of coronary occlusion–reperfusion, postconditioning (cycles of re-occlusion–reperfusion are

delivered after an ischemic index event), the remote ischemic conditioning of a limb (using arm cuff inflation–deflation cycles), and pharmacological cardio protection (achieved by the intracoronary delivery of adenosine or nitrates and the intravenous delivery of beta-blocker or cyclosporine A just before or at early reperfusion).

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