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Heart failure is the most negative consequence of CABG surgery (importance of exercise rehabilitation approach)

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Abstract

BACKGROUND: Statistics indicate that approximately 25,000 open-heart surgeries are performed annually in Iran, with coronary artery bypass grafting (CABG) surgeries accounting for 50–60% of these procedures. Although CABG offers numerous benefits to patients with coronary artery disease (CAD), some cases have reported negative consequences, such as heart failure (HF).

METHODS: This study explored several influential blood indices related to HF following CABG surgery using manuscripts extracted from PubMed, Scopus, and Google Scholar. The analysis focused on indicators that can exacerbate HF, including fibrotic factors such as catecholamines and the renin-angiotensin-aldosterone system (RAAS).

Conversely, it also investigated anti-fibrotic factors, including adrenomedullin (ADM), the natriuretic peptide system (NPS), NP-converting enzymes, and NP receptors. Additionally, the study evaluated the impact of various exercise training programs on these variables.

RESULTS: Some fibrotic factors, such as catecholamines and the RAAS, contrast with anti-fibrosis factors, including NPs, their producing enzymes, receptors, production and excretion processes, ADM, and others. Research suggests these elements can be positively influenced by exercise rehabilitation.

This study highlights the beneficial effects of exercise rehabilitation, specifically in reducing fibrotic factors and enhancing anti-fibrosis factors.

CONCLUSION: All types of exercise training—including endurance, resistance, and combined training, in both continuous and interval modes with moderate and high intensity—can delay fibrotic pathways after surgery and prevent subsequent adverse structural (pathologic hypertrophy) and functional changes in the heart, such as HF.

Keywords: CABG Surgery; Heart Failure; Exercise Rehabilitation; Fibrotic Factors; Anti-Fibrotic Factors

Introduction

Cardiovascular diseases, especially coronary artery disease (CAD), are the leading cause of death globally, accounting for 50% of all fatalities in developed countries approximately 5 million out of 12 million deaths[1]. Efforts to reduce mortality rates include developing various drug treatments, clinical care, and surgeries such as coronary artery bypass grafting (CABG). While CABG can provide some recovery, it may also lead to complications and long-term mortality[2].

Therefore, it is crucial to consider additional approaches, such as exercise training within cardiac rehabilitation (CR) programs after surgery, to prevent complications and expedite the recovery process. Numerous studies have demonstrated the benefits of these programs for this patient population[3-5].

However, most studies have focused on the general impact of traditional rehabilitation programs, specifically moderate-intensity continuous training, on performance indicators, exercise capacity, and tolerance in these patients[6-9]. Only a few studies have compared the effects of different types of exercise training on side-effect mechanisms, treatment processes, and recovery[10,11].

Given the importance of exercise rehabilitation programs for patients, more research is necessary to pinpoint the features of effective exercise training and improve these programs by clarifying their specific effects on recovery and complication prevention.

HF after CABG Surgery

CABG improves blood supply to the heart by using vessels from peripheral organs to bypass blocked coronary arteries, significantly reducing mortality from CAD. However, CABG can lead to complications such as calcification, re-occlusion, myocardial infarction, atrial fibrillation, and HF. Among these, HF is particularly concerning, often resulting in death due to the heart's inability to effectively fill or pump blood[2]. HF is a complex issue, with hypertension and concentric cardiac hypertrophy being major risk factors. Key predictors of HF and mortality post-CABG include a left ventricular mass index (LVMI) over 116 g/m² and a relative wall thickness (RWT) to end-diastolic dimensions ratio greater than 0.42[12].

Risk factors and exacerbation of HF after CABG

Key risk factors for complications after CABG include age over 55, chronic diseases like COPD and diabetes, lipid disorders, chronic renal insufficiency, peripheral artery disease (PAD), smoking, hypertension, and pathological ventricular hypertrophy[13]. Among these risk factors, high blood pressure and pathologic cardiac hypertrophy are two vital factors in causing and aggravating the complication of HF after CABG.

1- Hypertension

Hypertension can cause a range of pathological changes in the heart due to increased afterload. High blood pressure is associated with a rise in vasoconstrictor factors, a decrease in vasodilator factors, fluid excretion disorders, and an increase in inflammatory and oxidative factors. These factors contribute to the pro-fibrotic activation pathways, such as the RAAS and transforming growth factor-beta (TGFB) pathways. These pathways ultimately increase stiffness and fibrosis in the heart, leading to pathologic hypertrophy, functional heart disorders, and HF[14-16].

2-Pathologic Hypertrophy of the Heart

Inflammation is a key factor in the development of pathological hypertrophy[17,18].

In pathologic hypertrophy, the heart's muscle mass increases, but its pumping ability and efficiency decrease. This occurs because fibrotic tissue replaces muscle tissue in the myocardium.

The RAAS hypertrophy pathway and TGF pathway contribute to cardiac fibrosis and pathological concentric hypertrophy by increasing extracellular matrix (ECM) proteins[19,20]. Pathological hypertrophy significantly raises the risk of complications after surgery, making patients more susceptible to heart failure (HF) post-surgery.

Figures 1 and 2 illustrate the characteristics of concentric and eccentric hypertrophy[21]. Studies

have demonstrated the impact of exercise training on pathological hypertrophy and cardiac function in patients following CABG surgery.

For example, Zare Karizak et al. (2016) found that interval exercise training, compared to continuous exercise training, leads to a considerable reduction in concentric pathological hypertrophy and a notable improvement in systolic and diastolic function after CABG[22].

Some effective blood indices in HF after CABG surgery

1- Fibrotic factors

Catecholamines

Catecholamines, especially norepinephrine, are hormones released from the adrenal glands and postganglionic neurons in the somatic nervous system (SNS). They significantly contribute to the pathology of HF. In heart disease and after surgery, increased sympathetic activity helps improve weakened heart contraction due to inflammation. However, prolonged elevation of sympathetic activity ultimately worsens the condition and can lead to HF. Long-term catecholamine stimulation reduces the number and sensitivity of beta-adrenergic receptors, causing cardiac dysfunction. Additionally, increased sympathetic activity raises pressure on the heart, leading to compensatory hypertrophy, which is another factor in the development of HF[23].

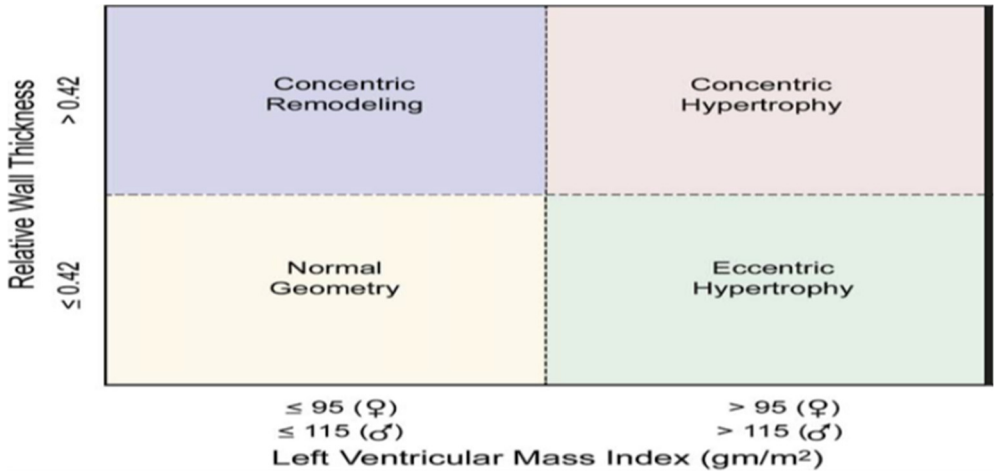

Figure 1. The criteria for distinguishing eccentric and concentric hypertrophy using the RWT index **[21]**

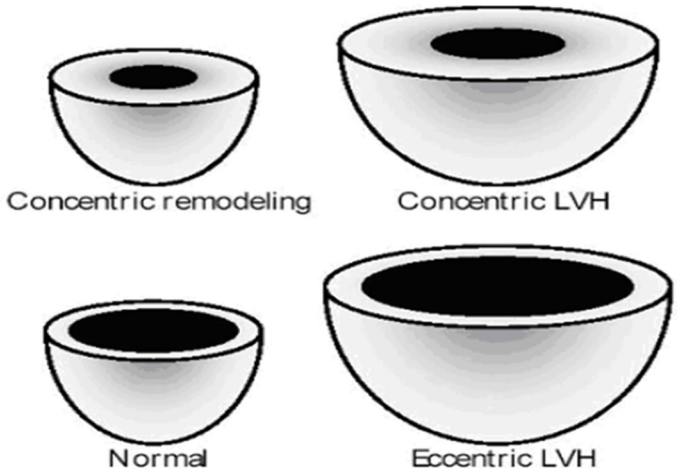

Figure 2. The shape of the ventricle in normal states and types of hypertrophy [21]

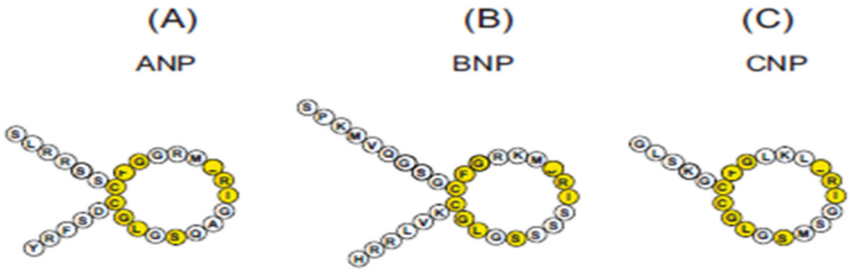

Figure 3. The biochemical and molecular structure of NPs [34]

RAAS

After cardiac surgery, blood reperfusion in the ischemic myocardium generates free radicals that trigger inflammation and pro-inflammatory cytokines like IL-6. This phenomenon reduces myocardial contractility and leads to a decline in cardiac output[18]. As cardiac output and blood volume decrease, the RAAS is activated. Renin secretion in the kidneys converts angiotensin to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme.

Angiotensin II causes increased vasoconstriction, creating pressure overload on the heart and promoting compensatory hypertrophy. It also stimulates aldosterone release and increases sodium and water reabsorption, causing volume overload. This overload initiates negative remodeling and fibrosis in the heart, ultimately leading to functional failure[24].

The inappropriate activation of the sympathetic and RAAS systems has wide-ranging negative effects on hemodynamic changes, ultimately contributing to the gradual progression of congestive HF (CHF)[24].

2- Anti-HF Indicators (Anti-Fibrotic Agents)

Adrenomedullin

ADM is a peptide widely distributed in the body's tissues and organs, particularly in the cardiovascular system. This peptide is primarily released from the medulla of the adrenal gland, where catecholamines are secreted[20]. ADM has various systemic and local effects on blood vessels and the heart. It acts as a potent vasodilator, with intravenous injection causing a rapid and significant reduction in blood pressure and decreasing total peripheral resistance. ADM increases stroke volume, causing a secondary increase in cardiac output by reducing the overload on the heart[25].

The vasodilation effects of ADM are not only systemic but also local, improving organ blood circulation, such as in the brain, kidney, lungs, and coronary arteries. The vasodilator effect of ADM occurs through at least two mechanisms:

1. A direct effect on vascular smooth muscle cells
2. An indirect effect on vascular endothelial cells

ADM has a diuretic and natriuretic role, making it effective in reducing blood pressure[25].

Additionally, ADM helps regulate vascular cells by preventing the proliferation of vascular smooth muscle cells and preventing the apoptosis of endothelial cells. ADM plays a key role in promoting angiogenesis pathways, which provide protection against ischemia and vascular damage. Furthermore, ADM regulates and suppresses negative cardiac remodeling by inhibiting hypertrophy pathways, such as the angiotensin II pathway, preventing the synthesis of ECM-forming proteins[20].

ADM is released by the heart in response to stimuli such as hypoxia, oxidative stress, and inflammatory cytokines, making it a key autocrine and paracrine regulator in cardiac disorders[20]. For this reason, it is regarded as an essential biomarker in all types of cardiovascular diseases. ADM levels increase with hypertension as a defense mechanism in the body[25]. Additionally, ADM levels rise in patients with HF, where they correlate positively with natriuretic peptide (NP) grades and norepinephrine and

negatively with cardiac ejection fraction (EF)[20].

Due to its sensitivity to inflammation, an integral component of atherosclerosis, ADM is considered one of the most critical predictors of coronary and peripheral artery disease, with greater predictive value than CRP, IL-6, and adiponectin.

ADM levels reflect the severity of cardiovascular damage and dysfunction across all related diseases, increasing compensatorily as the body attempts to counteract these disorders.

Zare Karizak et al. (2019) compared plasma ADM levels, ventricular EF, and resting rate-pressure product (RPP) in CABG patients who underwent high-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT). Their findings revealed no difference in plasma ADM levels between the two groups; however, HIIT was more effective than MICT in improving cardiovascular function after CABG surgery[26].

NPS

The system of natriuretic peptides (NPs), originally secreted from the heart and blood vessels, consists of three main components: NP type A, type B, and type C, along with guanylyl cyclase receptors, which are found throughout the body, especially in the cardiovascular system[27].

Therefore, these peptides have both local effects on the heart and systemic impacts on the endothelium of blood vessels and kidneys.

The effects of NPs include vasodilation, diuresis, natriuresis, prevention of fibrosis, hypertrophy, angiogenesis, and inflammation[28].

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) regulate blood pressure and reduce heart strain. They promote fluid movement away from blood vessels, lower sympathetic tone, dilate arteries, increase glomerular filtration, and suppress the renin-aldosterone system. These actions decrease blood pressure, reduce the heart's preload and afterload, minimize stress, and prevent compensatory hypertrophy, which aids in the long-term prevention of heart failure[29].

NPs, especially ANP and BNP, are key indicators of cardiovascular diseases. CNP plays a protective role in diseases such as atherosclerosis by preventing neointimal formation in damaged vessels following angioplasty, thus reducing the risk of re-clogging[30]. Elevated levels of these peptides correlate with structural changes and dysfunction in the heart, such as pathologic hypertrophy[31-33]. NPs play a protective role during various cardiovascular conditions and surgical procedures by responding to pressure overload, volume changes, ischemia, inflammation, and oxidative stress. Their increase helps counteract complications, making them important biomarkers for diagnosing and predicting cardiovascular issues, including hypertension, pathologic hypertrophy, pulmonary hypertension, and heart-kidney failure[20].

Types of NP receptors

NP receptors are widespread throughout the body, particularly in the heart, vascular endothelium, and kidneys. These receptors, known as guanylyl cyclase receptors, come in three types: NP receptor type I (NPR-A), NP receptor type II (NPR-B), and NP receptor type III (NPR-C). The first two receptors are responsible for the majority of biological actions.

ANP and BNP bind to NPR-A and elicit their functions, while CNP specifically binds to NPR-B, which is primarily localized in the heart and blood vessels, exerting local actions of NPs[35]. Downstream of these receptors, cyclic guanosine monophosphate (cGMP) serves as a secondary messenger that regulates NP actions[35].

Distinct from the first two receptor types, NPR-C operates differently. Rather than initiating biological functions, NPR-C is responsible for the removal and clearance of NPs[36].

NP Converting Enzymes

NPs are produced from precursor molecules through the action of enzymes that cleave the larger precursor material. Key enzymes in this process include Corin and Furin. Corin is crucial for producing ANP and also aids in BNP production. Furin specifically contributes to CNP production and participates in BNP production as well[19].

CORIN Enzyme

Corin is a transmembrane trypsin-like protease composed of 1,032 amino acids, and its overall structure is similar to type II transmembrane serine proteases[19]. Although highly expressed in cardiomyocytes, Corin has also been detected in blood and kidney tissue in healthy individuals[37].

This enzyme is involved in the breakdown of inactive Pro-ANP to active ANP and inactive Pro-BNP to active BNP[37,38]. As a transmembrane enzyme, Corin is easily absorbed into the bloodstream. After cleaving precursor molecules on the membrane surface, the resulting Corin components are released into the bloodstream, making it easily detectable through a specific antigen[19].

Corin levels increase in various cardiovascular conditions, such as chronic hypertension, CAD, and HF, where the compensatory elevation of NP production is necessary. However, in advanced stages, Corin production may fail[37].

FURIN Enzyme

Furin, an intracellular endoprotease, is synthesized in the Golgi apparatus. It is primarily expressed in cardiomyocytes, fibroblasts, and endothelial vessels, although its presence has also been observed in the kidneys[19,39,40]. Unlike Corin, there is no evidence of Furin's presence in the bloodstream due to **its** intracellular nature**.**

While its principal role is to facilitate the conversion of inactive pro-CNP to active CNP, studies have shown that it also has a supporting role in the Corin-dependent conversion of inactive pro-BNP to active BNP[40].

Furin plays a crucial role in combatting fibrosis in disease conditions. It converts pro-CNP, which has local and anti-fibrotic properties**,** along with other pro-fibrotic proteins such as pro-TGFB to TGFB, pro-endothelin to endothelin, and pro-MMP1 to MMP1**.** Therefore, its role as an anti-fibrotic agent in diseases is complex and multifaceted[41].

PRO-BNP/CORIN System

The PRO-BNP/CORIN system involves the conversion of inactive Pro-BNP to active BNP, which consists of three main components: the precursor (pro-BNP), the converting enzyme (CORIN), and the final product (BNP)[37]. This system can be found wherever Pro-BNP and CORIN are present in the body, producing active BNP.

The presence of Pro-BNP and CORIN has been confirmed in the heart, kidneys, and blood, indicating that this system is active in all three locations and provides BNP for local or systemic needs[37]. Therefore, it is crucial to have the proper amount of all three components and ensure optimal conversion to compensate for various heart diseases, especially heart failure, where BNP plays a significant role in the disease pathology and prevention of its negative effects. The presence of an efficient BNP production system is necessary to make BNP readily available and compensate for the conditions caused by the disease. Zare Karizak et al. (2017) conducted a study comparing the effects of MICT and HIIT on the PRO-BNP/CORIN system in post-CABG patients. They found that HIIT, compared to continuous training, improved the PRO-BNP/CORIN system after CABG surgery[42].

Failure in PROBNP/CORIN System and importance of it in HF

BNP has both direct (local) and indirect (systemic) effects in suppressing fibrotic factors, preventing negative cardiac remodeling (pathologic hypertrophy), and ultimately reducing the risk of heart failure. Any dysfunction in the PRO-BNP/CORIN system indicates a failure in the production of active BNP, which accelerates the progression of heart failure by eliminating its protective effects[37].

Failure in this system can occur due to problems with any of its three components. Issues related to Pro-BNP include glycosylation, which prevents CORIN from binding to it and converting it into active BNP[43]. Additionally, excessive production or impaired breakdown of Pro-BNP can result in increased Pro-BNP levels and decreased active BNP production[44]. This failure can be referred to as PRO-BNP/CORIN system failure with Pro-BNP origin.

Corin-related defects involve a reduction in Corin production or excessive breakdown, often occurring as a negative feedback response to elevated BNP levels in advanced disease conditions. This leads to decreased availability of Corin for BNP production and subsequent failure to produce active BNP[19,45]. These issues can be referred to as PRO-BNP/CORIN system failure with CORIN origin.

BNP-related issues arise from an imbalance in system products, leading to a rise in BNP-degrading agents and a drop in NT PRO-BNP excreting agents. This results in a higher ratio of inactive NT PRO-BNP to active BNP, creating a situation known as the BNP paradox. In this case, even with high levels of BNP derivatives, their inactivity limits their beneficial effects. A second BNP paradox occurs when elevated BNP levels saturate its receptors, hindering binding to other BNPs[46]. All of these issues can be attributed to PRO-BNP/CORIN system failure due to BNP disorders.

Clearance of NPS

There are two main pathways for eliminating NP: enzymatic and non-enzymatic. The enzymatic pathway breaks down NP into smaller components, which are then excreted in urine. The non-enzymatic pathway involves NP binding to the clearance receptor NPR-C, resulting in glomerular excretion in the kidneys[28].

The disposal mechanisms for diuretic peptides, BNP, and their rate of decomposition are crucial factors in the pathology of various diseases. The enzymatic pathway comprises dipeptidyl peptidase four (DPPIV) enzymes, neprilysin (NEP), and insulin-degrading enzyme (IDE). Additionally, the non-enzymatic pathway primarily involves binding BNP to its scavenging receptors (i.e., NPR-C), followed by glomerular excretion in the kidney[47].

NT PRO-BNP is an inactive byproduct of BNP with fewer elimination routes, relying solely on renal filtration. BNP has a half-life of 20 minutes, while NT PRO-BNP has a half-life of 120 minutes. Typically, NT PRO-BNP levels in the blood are 2 to 3 times higher than those of BNP[28].

The proper production and disposal of BNP are crucial in post-CABG patients, as dysfunction in these processes can lead to heart fibrosis and hypertrophy, increasing the risk of heart failure.

Zare Karizak et al. (2023) studied BNP production and breakdown, focusing on the ratios PRO BNP/BNP and BNP/NT PRO-BNP to assess BNP dynamics in these patients undergoing cardiac rehabilitation. Their research found that inactivity disrupts BNP production and elimination pathways, while both moderate MICT and HIIT effectively improve these processes compared to inactivity[48].

The degree of structural and functional disorder of the ventricles

It has been shown that negative cardiac remodeling (changes in dimensions, thicknesses, ventricular mass) and systolic and diastolic function disorders have a direct relationship with NPs, including BNP. Since BNP is secreted from the ventricles, compared to other markers or other NPs, it can be a better indicator of ventricular structural and functional disorder[49]. In particular, studies have shown that people who have concentric pathologic hypertrophy or systolic, diastolic, or both disorders, compared to people with normal heart structure or function, have a higher level of BNP, which coincides with an increased degree of disruption[49,50].

Exercise CR after surgery

CR is an acceptable therapeutic strategy to add to the basic medical program of patients with CAD, chronic and stable angina, after myocardial infarction, or after a variety of surgeries such as valvular surgery, PCI, or CABG. It has two main goals. First, it helps patients recover physical and mental abilities and perform activities related to daily life and work environment (with appropriate quality). Second, it prevents secondary complications related to the disease or after surgery, which can worsen the patient's condition or even lead to death[51].

The Component and Stages of CR

A comprehensive CR program includes six

main aspects: 1) initial patient assessment, 2) nutritional counseling and weight management, 3) continuous management of coronary risk factors, 4) psychological management, 5) physical activity counseling, and 6) exercise training[51]. In this regard, emphasizing the exercise training aspect of the CR program, there are four main stages for the patients' rehabilitation, especially those who have undergone surgery.

The rehabilitation program begins upon hospital admission, typically 7 to 14 days post-surgery. The first stage focuses on education and psychological support to enhance morale and reduce anxiety while informing patients about rehabilitation goals. The second stage involves an exercise training program after hospital discharge, with 2 to 3 sessions per week for 2 to 3 months, each lasting 1 to 2 hours under staff supervision and ECG monitoring. The third stage is a home exercise program lasting 6 to 12 months. Finally, the fourth stage is a long-term follow-up that lasts until two years post-surgery, which includes lipid profile check-ups every six months, along with examinations and reviews by a doctor and a psychiatrist. Continuous exercise training and risk factor management are essential in this stage[52]. The risk level of heart disorder is determined, based on the information in the patient's file, including the severity of the disease, age, physical fitness level, changes in heart rate, and ECG at rest and during exercise testing[53].

Types of Exercise Training in Rehabilitation Program

Exercise training is an integral part of the rehabilitation program for heart patients. The general effects of exercise training on this group of patients include increasing exercise tolerance, improving hemodynamics, enhancing ventilation efficiency and autonomic function, reversing muscle atrophy, and correcting endothelial, bioenergetic, and histological disorders, among others[54]. In the past, due to limitations and concerns for cardiac patients, the rehabilitation program primarily consisted of very light and continuous types of exercise training. However, with the accumulation of research findings over time, it has been discovered that different types of exercise training with various methods and intensities can be employed in the rehabilitation program for cardiac patients.

Rehabilitation specialists incorporate continuous, interval, resistance, and combined training into their programs today. The characteristics of these types of exercise training are described as follows.

MICT

Continuous training involves exercising uniformly for a long duration at a light to moderate intensity. This approach was previously used in rehabilitation centers, utilizing treadmills and ergometers. The low intensity of continuous exercise training makes it a safe choice, particularly for high-risk patients, those with minimum functional capacities, or individuals unable to perform high-intensity exercises.

Continuous exercise training is recommended to increase aerobic or functional capacity and reduce fat mass and other risk factors in cardiovascular patients[51]. However, one drawback of continuous training is its extended duration, which may lead to general muscle fatigue.

HIIT

This type of exercise consists of alternating bouts of high-intensity exercise and active or passive recovery bouts of low to moderate intensity between the high-intensity periods. This mode of training is commonly performed on treadmills and ergometers. While exercise intensity remains a controversial topic, accumulating evidence indicates that HIIT poses little risk to cardiac patients and is associated with minimal hemodynamic, electrical, biological, ischemic, or arrhythmic disturbances. HIIT has emerged as a vital care strategy for cardiovascular patients[54,55]. The interval nature of this exercise type allows patients to have active rest periods between high-intensity exercises, making them more manageable and enabling patients to benefit from their positive effects. However, there is still no unanimous agreement on interval

Table 1. Summary of articles

Authors/year	Study	Main Findings
Zare Karizak et al. 2023 [48]	HIIT and MICT training / The ratio of $ProBNP_{1-108}$/ BNP_{1-32} and NT-pro-BNP_{1-76}/BNP_{1-32}	Both HIIT and MICT, compared with inactivity, have positive effects on ratios of $ProBNP_{1-108}$/ BNP_{1-32}, NT-pro-BNP_{1-76}/BNP_{1-32} and could be effective in promoting the health of coronary arteries and prevention of HF in post-CABG patients.
Zare Karizak et al. 2021 [26]	HIIT and MICT training / ADM, Ejection Fraction (EF), Rate Pressure Product (RPP)	There was no difference between the effects of interval and continuous training on plasmatic ADM, but interval training had more effect than continuous training on the improvement of cardiac function after CABG surgery.
Zare Karizak et al. 2017 [22]	Aerobic Interval training (AI) and Aerobic Continuous training (AC) / concentric pathologic hypertrophy, systolic and diastolic function	(AI) training in contrast to (AC) training is more effective in decreasing concentric pathologic hypertrophy and improving systolic and diastolic function after Coronary Artery Bypass Grafting surgery.
Zare Karizak et al. 2017 [42]	Aerobic Interval training (AI) and Aerobic Continuous training (AC) / PRO-BNP/CORIN system	(AI) training, in contrast to (AC) training, is more effective in PRO-BNP/CORIN system development after CABG[42].
Billie Schulté et al. 2022 [60]	HIIT Versus MICT after Coronary Artery Bypass Graft	Both training methods provide improvements in cardiorespiratory fitness and QoL, with greater increases from HIIT.
Shafiee et al. 2023 [61]	HIIT and MICT in CABG patients	Both HIIT and MICT may be useful for the recovery of CABG patients.
Kakuchaya et al.2019 [62]	HIIT Versus MICT after CABG Surgery	HIIT proved to be as safe as a MICT in patients after CABG. It appeared to be significantly superior to MICT in improving cardiorespiratory fitness.
Ghardashi-Afousiet al. 2018 [63]	HIIT and MICT after CABG/ HRV, hemodynamic and echocardiography indices	HIIT has a greater effect on the improvement of cardiac autonomic activities after CABG.
Andersen et al. 2014 [64]	Soccer training (aerobic exercise training) / EF, diastolic function, and blood pressure	Six months of soccer training increased LVEF, diastolic function, and decreased blood pressure in inactive hypertensive men.
Barnet et al. 2014 [65]	Coronary artery bypass grafting (CABG) surgery / Hypertension ,concentric pathologic hypertrophy, corin, BNP	Hypertension and concentric pathologic hypertrophy were the most important risk factors in the development of HF after CABG, and Corin decreased despite the increase in BNP.
Chaudhry et al. 2013 [12]	Kidney Failure and Peripheral Vascular Disease Effect on Complications after CABG /Hypertension and Concentric Pathologic Hypertrophy	Hypertension and concentric pathologic hypertrophy are the most important risk factors in the development of HF after CABG.
Gladysheva et al. 2013 [66]	Corin overexpression increases cardiac function and survival in mice with cardiomyopathy.	Induction of corin increased cardiac function and survival (the importance of PRO-BNP/CORIN as a therapeutic target in HF was demonstrated)
Guiraud et al. 2012 [54]	HIIT and MICT training / cardiac structure and function and sports performance	Compared to moderate continuous exercise training, HIIT caused more improvement in the structure and cardiac and sports performance of cardiac patients.

Continued Table 1. Summary of articles

Authors/year	Study	Main Findings
Siribaddana et al. 2012 [2]	Cardiac disorders in POST CABG patients	HF is the most important complication after CABG, which is associated with patient mortality.
Fernandes et al. 2011 [67]	A single session of Aerobic Exercise and 4 Months of Exercise Training / BNP	A single session of aerobic exercise increased BNP, but 4 months of exercise decreased it.
Ichiki et al. 2011 [21]	Corin is naturally present in the heart, kidney, and blood, and the process of converting PRO-BNP to BNP takes place in the blood.	The process of converting PRO-BNP to BNP (PRO-BNP/CORIN System) in the blood was also active like tissue and showed the importance of this system in HF pathology.
Fox et al. 2011 [68]	Elevated BNP after CABG predicts long-term decline in physical function	There was a direct and strong correlation between the increase in BNP after CABG and the development of HF in the next 5 years of the patient.
Pitsavos 2011 [69]	Moderate-intensity continuous training / left ventricular mass, exercise performance capacity, and blood pressure in low to moderate-hypertension men	16 weeks of continuous training with moderate intensity reduced blood pressure and ventricular mass in hypertensive subjects.
Smart et al. 2010 [70]	Aerobic and Resistance Training / BNP and NTPRO-BNP in patients with HF	Adaptation to all kinds of sports training causes a reduction of BNP and NTPRO-BNP.
Dong et al. 2010 [71]	Plasma soluble corin and BNP production in patients with HF	The reduction of plasma corin in proportion to the severity of HF caused failure in BNP production.
Horio et al. 2008 [20]	Cardiovascular disease indicators: focusing on natriuretic peptides (BNP) and adrenomedullin.	BNP is an indicator of cardiovascular diseases and increases significantly in hypertension, concentric pathologic hypertrophy, and HF.
Wisløff et al. 2007 [11]	More cardiovascular effects of interval training compared to continuous training in patients with HF	8 weeks of high-intensity interval training was associated with more positive effects on endothelial function, reduction of pathologic cardiac hypertrophy, and reduction of BNP in patients with HF compared to moderate-intensity continuous exercise training
Stewart 2005 [72]	Exercise Training and Blood Pressure in the Elderly	Activity with more intensity than 75% vo_2 peak does not have a double effect on reducing blood pressure in hypertensive patients, and in this context, the priority is still moderate-intensity activity.
Aronson et al. 2002 [73]	Systolic Hypertension is Associated with Negative Complications after CABG	Systolic hypertension (over 140 mmHg) was associated with 40% mortality in POST CABG patients[72].
Hawkridge et al. 2005 [74]	Evidence on the absence of BNP in advanced conditions of HF disease	In advanced conditions of HF disease, BNP production fails and decreases

exercise training for individuals with the lowest functional capacity or high cardiovascular risk.

The Benefits of HIIT in Comparison to MICT

The benefits of HIIT compared to MICT are attributed to two main differences: Higher intensity and the interval nature of the training. HIIT provides a more intense training stimulus *vs.* MICT, leading to greater central and peripheral adaptations that result in more positive effects on cardiovascular structure and function, as well as aerobic and anaerobic capacity[54]. The high intensity of HIIT, which is associated with increased ischemia due

to stronger muscle contractions and more pressure on the blood vessels, stimulates hypoxia-inducible factor (HIF) and subsequently promotes the activation of PGC1α. PGC1α is known to enhance mitochondrial biogenesis, metabolism enzymes, glucose uptake, capillary formation, and antioxidant defense mechanisms (preventing the loss of O_2 in the form of free radicals). The improved motor economy and efficiency (anti-inflammatory defense and resistance to age-related sarcopenia) partly explain the superiority of HIIT over MICT[56]. In addition, the superior effects of HIIT compared to MICT on cardiovascular structure and function changes have been proven in patients and healthy individuals[11]. HIIT improves blood flow to the heart, reduces vascular endothelial disorders, decreases vascular resistance, and enhances sensitivity to calcium (Ca^{+2}), leading to increased contractile function of the heart in cardiac patients[54].

Moreover, the interval nature of HIIT activates mechanisms that contribute to its superiority over MICT. Periods of active rest or passive recovery between high-intensity exercise bouts reduce ischemia, increase muscle oxygenation, and enhance the regeneration of phosphocreatine reserves depleted during high-intensity periods. Consequently, fatigue is reduced, and the tolerance threshold for subsequent high-intensity exercise bouts is increased[54].

HIIT generally leads to more neurological, muscular, and cardiac adaptations *vs.* MICT for cardiac patients. However, concerns regarding the risk of sudden death during HIIT in cardiac patients have been addressed by studies (only 1 in 5 million cases)[54].

Resistance Exercise Training

Resistance training involves contracting different muscle groups to perform movements against resistance, such as body weight, weights, or resistance devices[57]. It helps improve body composition by preventing muscle loss and increasing muscle mass. Additionally, it enhances strength, boosts performance, and delays fatigue through increased capillary volume and muscle mass.

This type of training is especially beneficial for ischemic heart patients, who often lose muscle strength and mass following CABG surgery.

Incorporating resistance training into the rehabilitation program is therefore recommended for increasing muscle strength and aerobic capacity in this patient population[51]. However, caution should be exercised in prescribing resistance training for cardiac patients due to the potential increase in cardiac remodeling, ischemia, or arrhythmia associated with the elevated cardiac workload. It is also advisable to use light to moderate weights and emphasize the importance of not holding one's breath during resistance exercises[58].

Combined Exercise Training (Aerobic Training + Resistance Training)

In recent years, studies have investigated the role of various exercises in rehabilitation programs for cardiac patients. The strengths and weaknesses of different exercise training methods have been largely identified.

For example, moderate-intensity continuous training (MICT) improves cardiac function and exercise capacity in patients. This type of training also partially prevents post-surgical complications and enhances quality of life, particularly for weaker patients with acute disorders. In this sense, it has been introduced as a safe exercise training method[51].

However, due to its relatively long duration, MICT not only causes local and general fatigue in the patient but also becomes psychologically exhausting and, at times, unbearable due to a lack of variety.

On the other hand, resistance exercise training improves performance and overall patient condition by increasing muscle strength and preventing complications related to muscle wasting in post-operative life. Given the direct effects of this type of exercise, research has shown that resistance exercise training should be carefully prescribed for cardiac patients, taking into account their hemodynamic state,

cardiac load, and the possibility of negative cardiac remodeling[58].

Therefore, researchers have sought to diversify rehabilitation programs by incorporating both endurance and resistance exercises into combined training protocols. This approach helps reduce fatigue caused by continuous training and prevents potential negative effects from excessive or heavy-load resistance training[59]. Researchers have enhanced rehabilitation programs by incorporating both endurance and resistance exercises. This combination reduces fatigue from ongoing training and mitigates the drawbacks of heavy resistance training[59].

Studies indicate that this mixed approach outperforms endurance or resistance training alone in improving cardiac structure, exercise function, quality of life, and certain blood factors related to the disease in rehabilitating patients. However, opinions vary on the optimal intensity, duration, and ratio of exercises in combined training.

Conclusion

Several studies have demonstrated the favorable effects of cardiac exercise rehabilitation in POST CABG patients, and investigations have been conducted to explore the modifiability of cellular-molecular pathways and hormones that contribute to the structural and functional changes of the heart after CABG surgery. Based on the results of these studies, all types of exercise training, including endurance, resistance, and combined training in continuous and interval modes with moderate and high intensity, can delay the fibrotic pathways that occur after surgery and subsequently lead to adverse structural (pathologic hypertrophy) and functional changes in the heart, such as HF. For instance, some fibrotic factors, such as catecholamines, the RAAS, and others, in contrast to some anti-fibrosis factors, such as NPs and their producing enzymes, their receptors, their production and excretion processes, ADM, and so on, have been reported to be affected by exercise rehabilitation. This study primarily highlights the positive effects of exercise rehabilitation in reducing fibrotic factors and increasing anti-fibrosis factors. Table 1 indicates the summary of articles in this field.

However, as the range of fibrotic and anti-fibrotic factors that are effective in HF is extensive, further studies are required to investigate the impact of exercise rehabilitation on various fibrotic and anti-fibrotic pathways that are effective in HF to clarify the role of exercise rehabilitation on those pathways.

Conflict of interests

The author declares no conflict of interest.

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Author's Contributions

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