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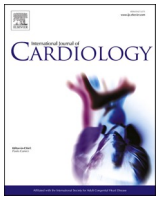

Epigenetic mechanisms underlying the beneficial effects of cardiac rehabilitation. An overview from the working groups of "cellular and molecular biology of the heart" and "cardiac rehabilitation and cardiovascular prevention" of the Italian Society of Cardiology (SIC)

Valeria Visco [a,1], Maurizio Forte [b,1], Francesco Giallauria [c], Luca D'Ambrosio [d], Mara Piccoli [e], Gabriele G. Schiattarella [f,g,h], Costantino Mancusi [g], Nadia Salerno [i], Arturo Cesaro [j], Marco Alfonso Perrone [k,l], Carmine Izzo [a], Francesco S. Loffredo [j], Michele Bellino [a], Edoardo Bertero [m,n], Nicola De Luca [g], Kalliopi Pilichou [o], Paolo Calabrò [j], Girolamo Manno [p], Elena De Falco [d], Albino Carrizzo [a,b], Valentina Valenti [q], Silvia Castelletti [r], Luigi Spadafora [s], Nidal Tourkmani [t,u], Antonello D'Andrea [v], Mario Pacileo [v], Marco Bernardi [w], Alessandro Maloberti [x,y], Beatrice Simeone [s], Gianmarco Sarto [s], Giacomo Frati [b,d], Cinzia Perrino [g], Roberto Pedrinelli [z], Pasquale Perrone Filardi [aa], Carmine Vecchione [a,b], Sebastiano Sciarretta [b,d,2,**], Michele Ciccarelli [a,*,2]

[a] *Department of Medicine, Surgery and Dentistry, University of Salerno, 84084 Fisciano, Italy*
[b] *IRCCS Neuromed, Pozzilli, Italy*
[c] *Department of Translational Medical Sciences, Federico II University, Naples, Italy*
[d] *Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy*
[e] *Cardiology Department, CTO Andrea Alesini Hospital, Rome, Italy*
[f] *Max Rubner Center for Cardiovascular Metabolic Renal Research, Charité -Universitätsmedizin Berlin, Berlin, Germany*
[g] *Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy*
[h] *DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany*
[i] *Division of Cardiology, Department of Experimental and Clinical Medicine, Magna Graecia University, Catanzaro, Italy*
[j] *Department of Translational Medical Sciences, Division of Cardiology, University of Campania "L. Vanvitelli", Naples, Italy*
[k] *Division of Cardiology and CardioLab, Department of Clinical Sciences and Translational Medicine, University of Rome Tor Vergata, 00133 Rome, Italy*
[l] *Clinical Pathways and Epidemiology Unit, Bambino Gesù Children's Hospital IRCCS, 00165 Rome, Italy*
[m] *Department of Internal Medicine, University of Genova, Genoa, Italy*
[n] *Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino - Italian IRCCS Cardiology Network, Genoa, Italy*
[o] *Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, Padova 35128, Italy*
[p] *Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE) "G. D'Alessandro", University of Palermo, Palermo, Italy*
[q] *Department of Cardiology, Santa Maria Goretti Hospital, Latina, Italy*
[r] *Cardiology Department, Istituto Auxologico Italiano IRCCS, 20149 Milan, Italy*
[s] *ICOT Istituto Marco Pasquali, Latina, Italy,*
[t] *Cardiology and Cardiac Rehabilitation Unit, Mons. Giosuè Calaciura Clinic, Catania, Italy*
[u] *ABL, Guangzhou, China*
[v] *Unit of Cardiology and Intensive Coronary Care, "Umberto I" Hospital, 84014 Nocera Inferiore, Italy*
[w] *Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University, Rome, Italy*
[x] *Cardiology IV, "A.De Gasperis" Department, Ospedale Niguarda Ca' Granda, Milan, Italy*
[y] *School of Medicine and Surgery, Milano-Bicocca University, Milan, Italy*
[z] *Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine-Cardiology Division, University of Pisa, Italy*
[aa] *Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy*

* Corresponding author.
** Corresponding author at: IRCCS Neuromed, Pozzilli, Italy and Sapienza University of Rome, Italy.
E-mail addresses: Sebastiano.sciarretta@uniroma1.it (S. Sciarretta), mciccarelli@unisa.it (M. Ciccarelli).
[1] Valeria Visco and Maurizio Forte equally contribute.
[2] These authors are joint senior authors.

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ABSTRACT

The benefits of cardiac rehabilitation (CR) have been demonstrated in patients after myocardial infarction (MI), and in patients with chronic heart failure (HF). The core components of the CR program include improvement in exercise tolerance and optimization of coronary risk factors (i.e., lipid and lipoprotein profiles, body weight, blood glucose levels, blood pressure levels, and smoking cessation). Indeed, CR has been shown to improve exercise capacity, control of cardiovascular risk factors, quality of life, hospital readmission, and mortality rates. Nonetheless, pre- and clinical CR and exercise training models are an enormous source of potential beneficial mechanisms that can be exploited for cardiac disease therapy. Consequently, in this review, we aim to explore the unique benefits of CR in HF and coronary artery disease, focusing on the epigenetic mechanisms involved and their translational relevance. These mechanisms may represent novel therapeutic targets to promote functional recovery after cardiac injury, and non-coding RNAs could be predictive biomarkers for CR success in patients.

1. Introduction

Cardiac rehabilitation (CR) is a multicomprehensive intervention involving patient evaluation, education, risk factor modification, and psychological support [1–4]. All available data have shown that CR programs improve essential patient outcomes, such as exercise capacity, cardiovascular (CV) risk factors, quality of life (QoL), hospital readmission, and mortality rates [5–7]. Experimental evidence obtained in murine models of cardiac stress, such as mice with surgical-induced heart failure (HF) or myocardial ischemia/reperfusion (IR) injury, demonstrated that exercise training exerts beneficial CV effects by regulating several epigenetic mechanisms, both in cardiomyocytes and in non-cardiomyocytes [8–11]. Several non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lnRNAs) were reported to be modulated by exercise training, and histone modifications and DNA methylation also represent additional epigenetic mechanisms that mediate the cardioprotective effects of exercise. The improvement of cardiomyocyte survival, regeneration, and cardiac contractility and the reduction of maladaptive hypertrophy and apoptosis represent the main effects regulated by the epigenetic modifications induced by exercise. Notably, epigenetic changes observed in preclinical models are often recapitulated in patients undergoing exercise, where epigenetic mediators may represent potential biomarkers of CR. This review discusses the relevant literature regarding the effects of CR in clinically relevant models of HF and coronary artery disease (CAD), focusing on exercise-induced epigenetic signatures and their translational relevance, highlighting the gaps in knowledge and future research perspectives.

2. Overview of epigenetic mechanisms

Epigenetics studies inheritable changes in phenotypes and gene expression that happen without modifications to the DNA sequence [12]. Accumulating evidence suggests that alterations of epigenetic mechanisms are linked to the onset and development of several cardiovascular diseases (CVDs), such as HF, and several drugs were reported to improve cardiac function in mouse models of cardiac diseases, by acting on epigenetic mechanisms [12,13]. Epigenetic mechanisms include chromatin remodelling through DNA modifications (i.e., methylation) and histone modifications (i.e., acetylation), and post-transcriptional gene regulation mediated by non-coding RNAs (i.e., miRNAs, lnRNAs, circRNAs) [14] (Fig. 1).

2.1. DNA methylation

DNA methylation is a reversible process usually linked to gene silencing and occurs through a stable chemical modification performed by DNA methyltransferase (DNMT), in the presence of the methyl donor adenosyl-methionine. DNMT mediates the addition of a methyl group (-CH3) to the 5′ position of cytosine in a gene promoter to form 5-methylcytosines (5mCs). Genes can be hypermethylated or hypomethylated in response to exogenous stimuli, and DNA methylation typically occurs at cytosine followed by guanine, the so-called CpG islands. Methylation results in reduced interaction between transcription factors and their specific binding sites, with a consequent decrease in gene expression [15]. Several studies reported a different pattern of methylation in the aorta of patients with atherosclerosis or the left ventricle of patients with HF, compared to healthy subjects, as well as in animal models of cardiac stress [16]. The latter suggests that cardiovascular stress may operate through DNA methylation.

2.2. Histone modification

Histone proteins, which form the nucleosome around which DNA is wound, undergo different chemical modifications, among which acetylation and methylation are the most characterized [17,18]. Histone modifications may occur at many amino acid residue positions and are linked to the activation or repression of gene expression, resulting in the modulation of histone-DNA interactions that ultimately influence chromatin accessibility to transcription factors and DNA-binding elements [16]. For example, acetylation of histone 3 generally is linked to the activation of transcription [19]. Histone acetylation is mediated by histone acetyltransferases (HATs), whereas histone deacetylation is mediated by histone deacetylases (HDACs) [16]. The modulation of HATs and HDACs has a significant role in CVD since HDACs and HATs modulate many genes involved in cardiovascular function. For example, class II HDACs act as suppressors of the transcriptional program involved in cardiac hypertrophy and HF, and HDAC inhibition was reported to exert cardioprotective effects in several preclinical models of heart disease [20,21]. Histone methylation can either activate or inhibit the gene expression, usually occurring at the arginine residues [22].

2.3. RNA editing

Adenosine-to-inosine editing is an RNA modification catalyzed by the adenosine deaminase acting on RNA (ADAR) family of enzymes, in which adenosines in double-stranded or structured RNAs are deaminated. RNA editing influences coding potential, translation efficiency, and splicing, and several sites that undergo RNA editing have been characterized prevalently in introns and untranslated regions (UTRs) [23]. Several studies further demonstrated that alterations of RNA editing mediated by ADAR-1 and ADAR-2 are involved in several CVDs, such as atherosclerosis and adverse cardiac remodelling [24,25].

2.4. Non-coding RNAs

miRNAs and lncRNAs are well-characterized non-coding RNA molecules that participate in a myriad of biological functions, acting as post-transcriptional regulators of gene expression. miRNAs are small single-stranded noncoding RNAs of 18 to 22 nucleotides that, once maturated, interact with the 3′-untranslated region of a mRNA target (3’-

UTR), generally inhibiting protein synthesis. The latter occurs either by mRNA degradation or inhibition of translation. A single miRNA may regulate different genes depending on its base complementarity with the 3'-UTR of a target gene. In the cardiovascular system, several miRNAs have emerged to play a fundamental role in cardiomyocytes and non-cardiomyocytes, regulating several processes such as cellular growth, apoptosis, contractility and angiogenesis [26].

LncRNAs represent another interesting class of non-coding RNAs that have garnered significant interest due to their stronger relevance in cardiac pathophysiology. They include transcripts >200 nucleotides long that share many similarities with mRNA transcripts since they are transcribed by RNA polymerase II and can undergo capping, poly-adenylation, and splicing [27]. LncRNAs regulate gene expression by different mechanisms, which include chromatin modifications and the regulation of translation at different levels (splicing, stability and translation) [28]. LncRNAs also interact with transcription factors or act as a sponge for miRNAs [28]. Different studies suggest a link between genetic variants in genes coding for lncRNA and CVDs, such as myocardial infarction (MI) and coronary artery disease [29,30] and to date several lncRNAs were reported to be associated with cardiac hypertrophy and HF in experimental models (for a detailed review, see [31]).

Circular RNAs (circRNAs) are non-coding RNAs characterized by a covalent bond between the 3′ end of an exon and the upstream 5′ end of the same or another exon. Although the molecular mechanism by which circRNAs regulate gene expression is not entirely characterized, due to a lower expression compared to miRNAs and lncRNAs, it has been suggested that they act via sponging miRNAs or binding RNA-binding proteins [32]. Other reports also indicate the role of several circRNAs in the pathogenesis of CVDs, since they can regulate cardiac hypertrophy, inflammation, and cardiac fibrosis [33].

Since its possibility to detect non-coding RNAs in the blood, they are also emerging as potential diagnostic or prognostic circulating biomarkers for patients with CVDs [26,32,34].

3. Heart failure

Cardiac rehabilitation (CR) plays a crucial role in managing chronic heart failure (HF) patients, especially those who have recently been hospitalized due to exacerbations and disease progression [35,36]. CR programs and optimal medical therapy can reduce hospitalizations and improve QoL and exercise tolerance, although uncertainty persists about their effects on mortality [37–42]. The impact on hospitalization is predominantly seen in patients who are highly adherent to the exercise program [43].

Specifically, CR programs should assist HF patients in developing the skills to successfully self-manage their long-term condition [44], improve exercise capacity and health-related QoL, and complement the impact of drugs and devices in reducing hospitalizations [4,44].

A careful baseline assessment is required, and exercise intervention should only be initiated in clinically stable individuals [45]: there must be no contraindications to exercise, such as symptomatic hypotension or severe hypertension at rest or during exercise, unstable cardiac disease, uncontrolled arrhythmias, or deteriorating symptoms of HF [45]. Moreover, cardiopulmonary exercise testing (CPET) is essential to evaluate functional capacity, exercise-induced arrhythmias, and hemodynamic abnormalities and for the prescription of exercise intensity based on peak oxygen uptake (VO2peak) or resting and maximal heart rate (HR) during exercise [46–48]. However, in patients unable to perform a CPET, a 6-min walk test (6MWT) can be performed, while a sit-to-stand test could be necessary for patients unable to walk [49–51]. Furthermore, the exercise should be supervised through an exercise-based CR program, while non-supervised home-based sessions should be gradually added [52].

Exercise prescriptions usually follow a standardized protocol, such as the FITT (frequency, intensity, time duration, and type of exercise)

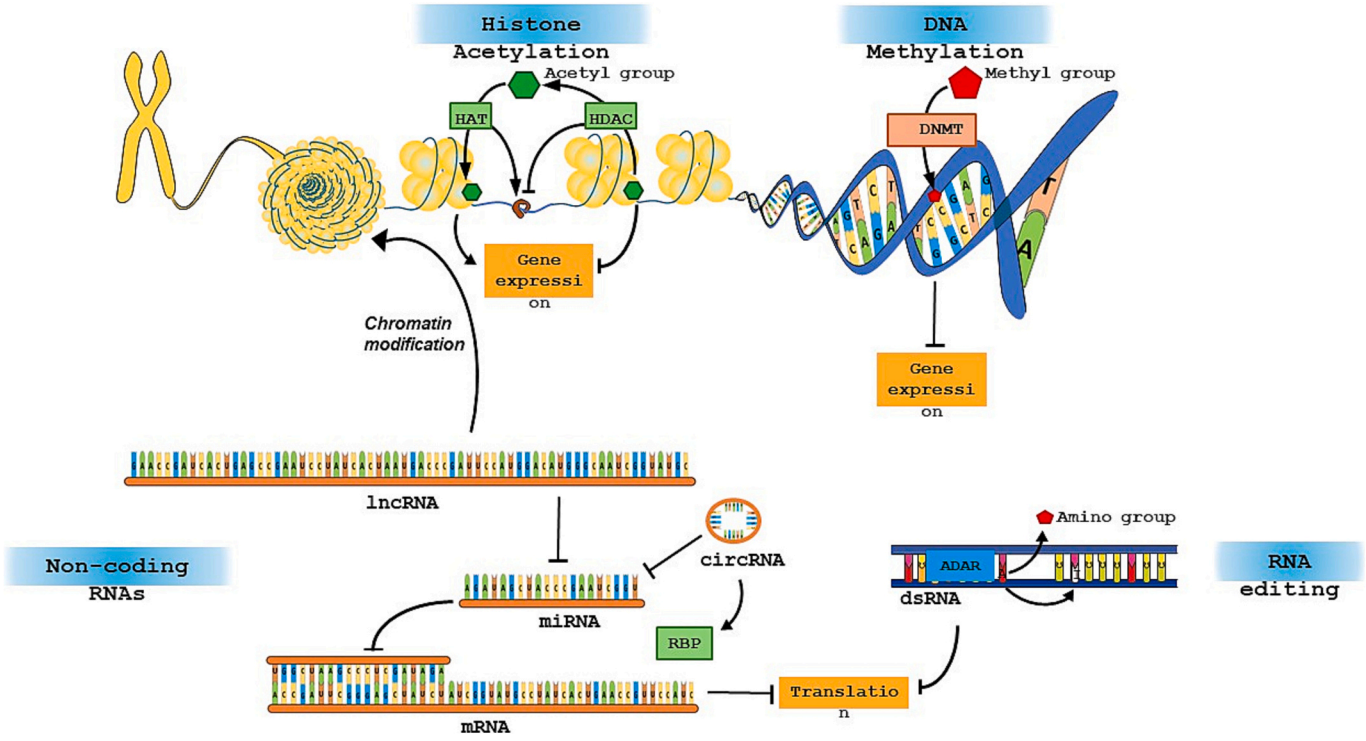

Fig. 1. Overview of epigenetic mechanisms. The figure illustrates the main epigenetic mechanisms regulated by exercise training: Histone acetylation, DNA methylation, non-coding RNAs and RNA editing. Legend: ADAR, adenosine deaminase acting on RNA; circRNA, circular RNA; DNMT, DNA methyltransferase; dsRNA, double strand RNA; HAT, histone acetyltransferase; HDAC, histone deacetylases; lncRNA, long non-coding RNA; miRNA, microRNA; RBP, RNA binding protein. See the text for details. This figure was generated in part using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

model, which can also facilitate comparisons of different real-world experiences; however, variance and disagreement among clinicians still exist [53].

Consequently, to optimize exercise prescription, the European Association of Preventive Cardiology (EAPC) has introduced a digital, interactive decision support tool: the EXPERT (EXercise Prescription in Everyday practice & Rehabilitation Training) Tool (https://www.escardio.org/Education/ Practice-Tools/CVD-prevention-toolbox/expert-tool) [54]. Overall, no exercise component significantly predicts mortality; only adherence to the whole intervention improves outcomes [55]. Consequently, identifying novel biomarkers associated with CR could be essential for effective biomarker-guided CR in HF patients.

3.1. From preclinical models to clinical scenario

The cardioprotective effects of exercise mediated by epigenetic mechanisms were extensively studied in clinically relevant models of HF, such as in rodents subjected to MI induced by permanent ligation of the left anterior descending artery (LAD), in those subjected to pressure overload (PO) induced by transverse aortic constriction (TAC), as well as in models of myocardial ischemia followed by reperfusion [8–11] (Fig. 2). These models resemble a condition of HF with reduced ejection fraction (HFrEF). Few studies also reported the involvement of epigenetic mechanisms in animal models of HF with preserved ejection fraction (HFpEF) undergoing exercise [56–58].

3.1.1. Molecular pathways activated by exercise in post-MI models

The epigenetic effects of exercise as a post-MI rehabilitation were documented in experimental models of MI.

Exercise lowers blood pressure and prevents microvascular rarefactions in hypertensive rats by rescuing levels of miRNA-16, −21, −126, three miRNAs targeting markers of apoptosis and angiogenesis, such as the antiapoptotic protein Bcl-2 and the vascular endothelial growth factor, respectively [59]. These findings suggest that a potential approach for preventing the progression of left ventricular hypertrophy could involve the modulation of specific miRNAs. Along with this evidence, the reduction of circulating levels of miR-21 was also observed in hypertensive patients undergoing moderate endurance training [60], while lower levels of miR-16-5p were reported in endurance and resistance athletes compared to sedentary individuals [61].

Another study demonstrated that miR-222 is involved in the ability of 8 weeks of running exercise to increase the endogenous capacity of the adult heart to regenerate. Exercise increases cardiomyogenesis in an extended border zone of the infarcted area of mice undergoing MI [11] through the upregulation of miR-222 [11,62]. Remarkably, miR-222 was reported to be upregulated in healthy young athletes immediately post-exercise (within 1 min of completion of exercise testing) [63] and in the serum of patients with HFpEF or HFrEF [64] undergoing CPET. Serum levels of miR-222 were also found to be lower in patients with MI, compared to healthy patients, and to correlate with increased rehospitalization or death during 1-year follow-up [62,63]. These results suggest that miR-222 may be considered a valid biomarker for evaluating the effects of cardiac rehabilitation in patients. The reduction of infarct size mediated by miR-122 following exercise is mediated by inhibition of Homeodomain-Interacting Protein Kinase 1 and 2 (HIPK1/2), a serine/threonine kinase involved in promoting apoptosis and suppressing cell proliferation. The downregulation of p53 mediates the cardiac protection observed in knockout mice for HIPK2 undergoing MI [65].

In addition to miR-222, another study found that 4-week swim training reduces apoptosis and improves cardiac function in mice undergoing MI via miR-1192 up-regulation [66]. The reduced expression in cardiomyocytes of caspase-3, a pro-apoptotic factor mediates the anti-apoptotic effects of miR-1192. However, the role of miR-1192 as a circulating biomarker should be validated in patients undergoing cardiac rehabilitation.

Diabetes increases the risk of developing HF following an MI. In diabetic mice undergoing MI, exercise was reported to reduce ventricular arrhythmias and restore cardiomyocyte calcium handling [67]. The beneficial effects in lowering diabetic cardiomyopathy are mediated by the up-regulation of miR-126, which in turn contributes to reducing its target, the anti-angiogenic factor sprout-related EVH1 domain-containing 1 (SPRED-1) [68]. Of interest, lower levels of miR-126 were observed in patients with myocardial infarction [69] whereas endurance aerobic exercise with moderate intensity or above was reported to increase circulating levels of miR-126. The protective effects of miR-126 in the cardiovascular system are mediated by multiple mechanisms, including anti-inflammatory, anti-apoptotic, pro-autophagic effects, and angiogenesis [70].

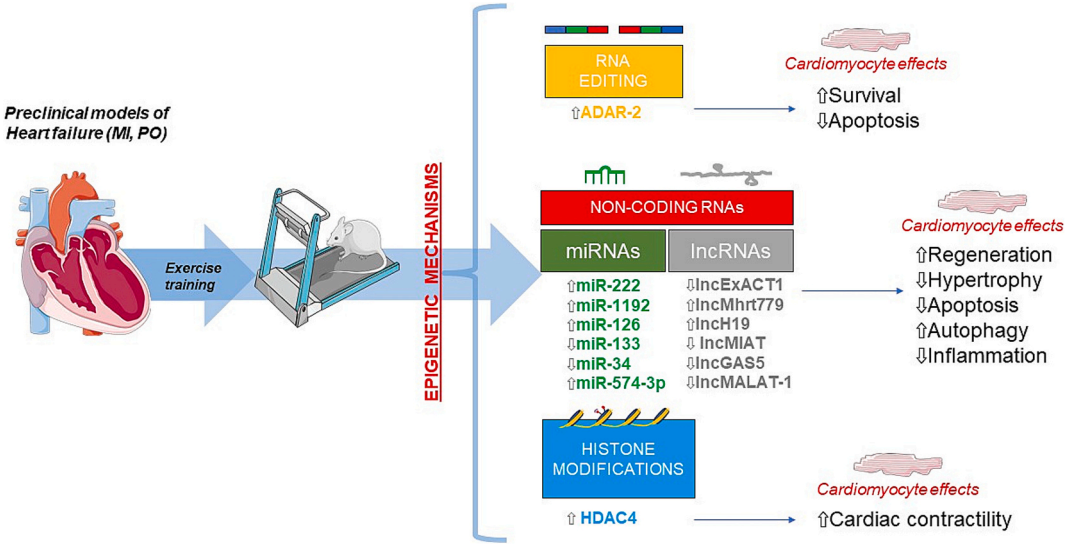

Fig. 2. Modulation of epigenetic mechanisms by exercise training in preclinical models of heart failure induced by pressure overload (PO) or myocardial infarction (MI). Exercise modulates different non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). The net result is the increase in cardiac regeneration and the reduction of apoptosis and maladaptive hypertrophy. Other epigenetic mechanisms include RNA editing and histone modifications. See text for further details. This figure was generated in part using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Yamada et al. [71] demonstrated that expression levels of two miRNAs regulating cell proliferation and apoptosis were significantly different in patients before CR compared with controls and patients after CR. Precisely, the expression of hsa-miR-125b-1-3p was significantly downregulated and that of hsa-miR-1290 was significantly upregulated in patients before CR. Consequently, CR could restore the expression of specific circulating miRNAs in HF patients.

Among lncRNAs, exercise training was reported in rats undergoing MI to rescue the expression of three lncRNAs regulating fibrosis and apoptosis, such as lncRNAs H19, myocardial infarction association transcript (lncMIAT), and growth arrest-specific 5 (lncGAS5) [72]. Another report found that exercise training improves cardiac function in rats subjected to MI by inhibiting lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1). The protective effects mediated by MALAT-1 inhibition include restoring autophagy and reducing apoptosis via the increased expression of miR-150-5p and the PI3K/Akt signaling [73]. Remarkably, higher levels of MIAT and MALAT-1 were found to be associated with cardiac ischemic events in patients [74]. MALAT-1 levels also correlate with the increase of endothelial dysfunction in obese children, while exercise decreases MALAT-1 levels [75]. Other post-transcriptional mechanisms modulated by exercise include RNA editing. 3 weeks of swimming were reported to upregulate the cardiac expression of ADAR2 in mice, an enzyme that edits adenosine to inosine nucleotides in double-stranded RNA. ADAR2 overexpression improves cardiac function in a model of MI and reduces doxorubicin-induced cardiomyopathy. Mechanistically, ADAR2 reduces miR-34a level, an inhibitor of genes exerting pro-survival and antiapoptotic effects, such as Sirt1, Cyclin D1, and Bcl2 [76]. These results suggest that ADAR2 mediates the beneficial effects of exercise in models of MI. However, it would be interesting to test whether ADAR2 inhibition mitigates the protective effects of exercise in this context.

The impact of exercise on histone modifications was also observed. In this regard, exercise was reported to improve mitochondrial function and increase glucose uptake in the heart of mice undergoing MI. The latter is mediated by AMP-activated protein kinase (AMPK)-induced phosphorylation of histone deacetylase 4 (HDAC4). Once phosphorylated, HDAC4 increases GLUT1 expression via upregulating GLUT1 promoter H3K9ac modification [77].

3.1.2. Molecular pathways activated by exercise in pressure overload-induced heart failure models

The effects of exercise were also studied in rodents undergoing pressure overload-induced by TAC, representing a relevant experimental model of HF caused by chronic arterial hypertension.

Exercise also modulates non-coding RNAs in this context. miR-133 was reported to be downregulated in the hearts of rats undergoing endurance exercise [78] and also in mice undergoing TAC. MiR-133 inhibition causes adverse remodelling and hypertrophy even without hypertrophic stimuli, suggesting that miR-133 mediates adaptive mechanisms of exercise. miR-133 exerts its effects through different targets, such as RhoA, a GDP-GTP exchange protein regulating cardiac hypertrophy, cell division cycle 42 (Cdc42), a signal transduction kinase involved in hypertrophy; and negative elongation factor complex member A, Whsc2 (Nelf-A/WHSC2), a nuclear factor participating in cardiogenesis.

A recent study showed that the improvement of myocardial remodelling by exercise in mice undergoing pressure overload was mediated by the increased expression of miR-574-3p, which in turn contributes to the inhibition of interleukin-6, a pro-inflammatory cytokine [79]. Exercise activates adaptive hypertrophy also through the upregulation of CITED4 (CBP [CREB-binding protein]/p300-interacting transactivators with E [glutamic acid]/D [aspartic acid]-rich-carboxyterminal domain), a transcription factor whose inhibition accelerates HF in models of pressure overload. CITED4 mediates adaptive hypertrophy by upregulating miR30d (microRNA 30d), which acts as a paracrine factor to suppress myofibroblast activation [80].

Finally, microR-423-5p might be a potential biomarker for assessing the therapeutic effect of cardiac rehabilitation on hypertensive patients with HF with a moderately reduced ejection fraction [81]. Precisely, in these patients, CR reduces the expression of circulating microRNA-423-5p, which plays a key role in cardiac development, acts as a biomarker of cardiac injury, and is implicated in left ventricular hypertrophy [81,82]. Moreover, Huang et al. showed a clear association between miR-423-5p expression and NT-proBNP, NYHA classification, 6MWT scores, LV parameters, and LVEF [81]. Nevertheless, a previous study excluded circulating miR-423-5p as a biomarker of systemic ventricular function after atrial repair in adults with transposition of the great arteries [83]. Consequently, miR-423-5p may only be effective in detecting the cardiac function of patients with HF.

Accordingly, Tijsen et al. [84] showed higher miR-423-5p serum levels in HF patients, compared to healthy individuals. Li and colleagues [85] compared the cardiac lncRNA landscape between sedentary mice, mice undergoing exercise, and mice subjected to TAC for 2 or 8 weeks to induce pathological cardiac hypertrophy or HF, respectively. Data showed that the long noncoding exercise-associated cardiac transcript 1 (lncExACT1) is downregulated by exercise while upregulated by TAC. Forced overexpression of lncExACT1 induces maladaptive hypertrophy and HF, whereas its inhibition rescues cardiac dysfunction in mice. Mechanistically, the authors observed that lncExACT1 binds to the promoter region of the dachsous cadherin-related 2 (DHCS2) and positively regulates its expression. DHSCS2 up-regulation inhibits yes-associated protein (YAP), a Hippo pathway component, exerting proliferative effects. Indeed, DHCS2 inhibition rescues YAP activity and inhibits STK4 serine/threonine kinase (MST1/2), the Hippo pathway's core kinases, and YAP inhibitors. These results suggest that exercise induces cardiomyogenesis and physiological hypertrophy, at least in part through YAP activation. In the same study, lncExACT1 expression was higher in heart samples from HF patients than in healthy subjects.

Another study demonstrated that exercise hypertrophic preconditioning (EHP) in mice undergoing pressure overload reduces myocardial hypertrophy by upregulating the lncRNA myosin heavy chain-associated RNA transcript Mhrt779 in the heart. This transcript acts as an inhibitor of the Hdac2 (histone deacetylase 2)/Akt/glycogen synthase kinase 3β (GSK3β) and -MHC signaling pathways. Mechanistically, exercise reduces the 3-methylation of histone 3 at the a4 promoter of Mhrt779, enhancing its expression [9].

Exercise exerts cardiac effects through additional epigenetic mechanisms, such as DNA/RNA methylation and histone modifications. In this regard, 2 weeks of aerobic running exercise increases the cardiac levels of the N-terminal proteolytically derived fragment of histone deacetylase 4 (HDAC4)-NT, a stress-responsive epigenetic repressor [86]. Cardiac HDAC4-NT level is instead reduced in mice subjected to pressure overload-induced HF. The latter indicates that HDAC4-NT is differentially regulated by physiological and pathological stress. Mice with cardiomyocyte-specific deletion of HDAC4-NT show a reduced exercise capacity characterized by cardiac fatigue. HDAC4 upregulation by exercise leads to downregulating NR4A1-induced hexosamine biosynthetic pathway (HBP) [86], thereby decreasing O-GlcNAcylation of fundamental proteins involved in cardiac contractility, such as STIM1. A reduced level of HDAC4-NT and an increase of O-GlcNAcylation were also reported in cardiac samples of patients with aortic stenosis or hypertrophic obstructive cardiomyopathy [86].

Another study investigated the effects of exercise on changes in methylation of adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), a fundamental inflammasome component [87]. Exercise increases ASC methylation in patients with HF, and this effect was associated with the reduction of interleukin-(IL)-1 level [87]. ASC methylation was also positively associated with a 6-min walk test in patients. These results suggest that exercise protects from HF development through the epigenetic regulation of inflammasomes [87].

3.1.3. Heart failure with preserved ejection fraction

HFpEF is the most common form of HF observed in older people. In aged mice, exercise training ameliorates diastolic dysfunction and pulmonary congestion, which are common HFpEF features [57]. In a mouse model of HFpEF, characterized by simultaneous metabolic and hypertensive stress, the cardioprotective effects of exercise were associated with changes in m6A RNA methylation of genes involved in myocardial energy metabolism [56]. Exercise also regulates genes involved in metabolic remodelling through epigenetic mechanisms in multiple tissues, such as skeletal muscle and adipose tissue. In this regard, exercise increases the expression of glucose transporter 4 (GLUT4) and peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1-α) through histone modifications in skeletal muscle [88]. Another study found that skeletal muscle of individuals undergoing exercise displays hypomethylation in promoters of genes involved in glycogen metabolism, glycolysis, and tricarboxylic acid cycle [89]. Exercise also reduces insulin resistance in mice by reducing the serum level of the lnRNA MALAT-1. The latter contributes to the increased expression of miR-382-3p, which reduces resistin level, a hormone released by adipocytes and responsible for insulin resistance in type 2 diabetes [90]. These results suggest that the improvement of whole-body metabolism by exercise may reduce the cardiovascular risk of individuals with lifelong physical activity.

Other evidence suggests that circulating levels of miR-181c and miR-126 may be considered biomarkers of the response to exercise training in HFpEF patients undergoing an exercise rehabilitation intervention. High miR-181c predicts reduced peakV·O2 response and low responders to exercise [91], whereas miR-126 levels increased after exercise rehabilitation and were positively correlated with peak oxygen consumption (peak VO_2) and the improvement of cardiac function [92]. miR-181c reduces the expression of Parkin-1, a marker of mitophagy, and SMAD-7 in cardiac fibroblast in vitro, suggesting that the reduction of mitophagy and pro-fibrotic activation may represent the molecular mechanisms by which miR-181c leads to HFpEF [93]. Further studies should analyze the molecular mechanisms regulated by miR-181c and miR-126 in experimental models of HFpEF. Nonetheless, further studies are needed to increase the knowledge of CR benefits in HFpEF.

4. Coronary artery disease

CAD is a significant issue for human health globally, representing the most prevalent CVD. According to the World Health Organization, CVD represents the principal cause of death [94], and several therapeutic advances have been made in recent decades to cope with the health burden of CVD [95]. However, therapy efficacy is highly dependent on post-acute phase recovery and vice-versa. For patients with CAD, CR is a critical element of treatment and should be considered not only as a supplement to treatment but also as a substantial component of the therapy and its continuation in the post-acute phase of the disease [96]. CR can significantly improve patients' physical strength and prevent or delay the worsening of CAD. CR treatment models have been extensively studied with each country's specific conditions and cultural background. Despite the well-recognized beneficial effects of CR on long-term CV and global outcomes, CR is underutilized by a significant portion of patients who, conversely, would widely benefit from it. Humphrey et al. found that CR was performed in less than 30 % of patients 1 month after acute MI in a cohort of 2096 patients [97].

Exercise training and the resulting enhancement of VO2peak and endurance capacity contribute significantly to the numerous advantages associated with CR. CR plays a fundamental role in extending the duration of physical activity and increases exercise tolerance and overall QoL in patients with CAD. Furthermore, CR mitigates angina and ischemia, leading to a reduction in hospitalizations and mortality rates [98–102].

CR also facilitates the rehabilitation of patients following Percutaneous Coronary Interventions (PCI) [103] and reduces cardiac events, hospital readmissions, and mortality after Coronary Artery Bypass Graft (CABG) [104].

Kim et al. demonstrated the effectiveness of hospital-based CR model in improving overall health status and minimizing rehospitalization. Their study revealed that CR in individuals with CAD leads to increased left ventricular ejection fraction and reduced mortality rates after 6 months of in-hospital CR [105].

In line with the same evidence, CR was reported to improve vascular endothelial function and reduce blood pressure [106]. Simultaneously, the utilization of early in-hospital CR can serve as a transitional phase for heart transplantation.

4.1. Myocardial ischemia/reperfusion injury: From preclinical models to clinical scenario

Myocardial ischemia/Reperfusion (I/R) injury occurs in patients with acute MI undergoing urgent revascularization, cardiac arrest, or during surgical procedures that require temporary cessation of coronary blood supply, such as in the case of PCI, CABG or cardiac transplantation [107,108]. The epigenetic mechanisms involved in the cardiac protection induced by exercise have been investigated in rodents undergoing surgical-induced I/R protocols [8,10] (Fig. 3).

The modulation of non-coding RNAs by exercise was also observed in models of I/R. Four-week swim training increased circulating levels of miR-342-5p in exosomes in rats, and cardiac-specific inhibition of miR-342-5p reduced the cardioprotective effects of swimming [8]. Mechanistically, miR-342-5p reduced pro-apoptotic signals by inhibiting Caspase 9 and Jnk 2 and increases pro-survival mechanisms by targeting AKT phosphorylation. Another interesting finding is the increased endothelial secretion of miR-342-5p following exercise, which exerted protective effects in cardiomyocytes through paracrine mechanisms, such as the reduction of apoptosis in response to hypoxia/reoxygenation [8]. Experimental data regarding the exosomal secretion of miR-342-5p were also confirmed in exercise-trained human volunteers [8]. It would be interesting to assess whether miR-342-5p can be considered a prognostic marker for patients undergoing CR after a surgical procedure.

Other miRNAs were also found to be regulated by exercise in models of I/R. These include miR-17-3p, which increases in the heart of mice undergoing exercise and contributes to cardiac growth by targeting metallopeptidase inhibitor 3 (TIMP3). miR-17-3p agomir administration mimics the protective effects induced by exercise in mice subjected to I/R injury [109]. Remarkably, an increased level of miR-17-3p was also found in the serum of patients with chronic HF undergoing exercise. In a recent paper [10], exercise was reported to increase the cardiac expression of miR-486 in mice undergoing I/R injury and to alleviate apoptosis by targeting PTEN and FoxO1 and activating the Akt/mTOR pathway.

An interesting study showed that exercise reduces the infarct size in mice undergoing myocardial I/R by increasing small extracellular vesicles (sEVs) secreted by brown adipose tissue. In particular, miR-125b-5p, miR-128-3p, and miR-30d-5p were identified as the sEV components mediating cardio protection by the suppression of the proapoptotic MAPK (mitogen-associated protein kinase) pathway [110]. In line with the same evidence, Barber and colleagues [111] found that 20 weeks of endurance exercise training increase circulating levels of miR-125b-5p and miR-30d-5p in volunteers. These results suggest that also non-cardiomyocyte cells may represent the source of microRNAs mediating the cardioprotective effects exercise.

In a mouse model of CAD, obtained by feeding ApoE/LDLR double knock-out mice with a western diet, exercise was observed to increase miR-20a levels, which in turn contributes to increased endothelial cell proliferation and to reduce molecular signaling involved in atherosclerosis [112]. However, whether exercise reduces CAD progression through miR-201 was not investigated in vivo [112]. Levels of miR-20a were found to be lower in endothelial cells isolated from patients with CAD [112]. In another model of atherosclerosis, the Apo E knockout

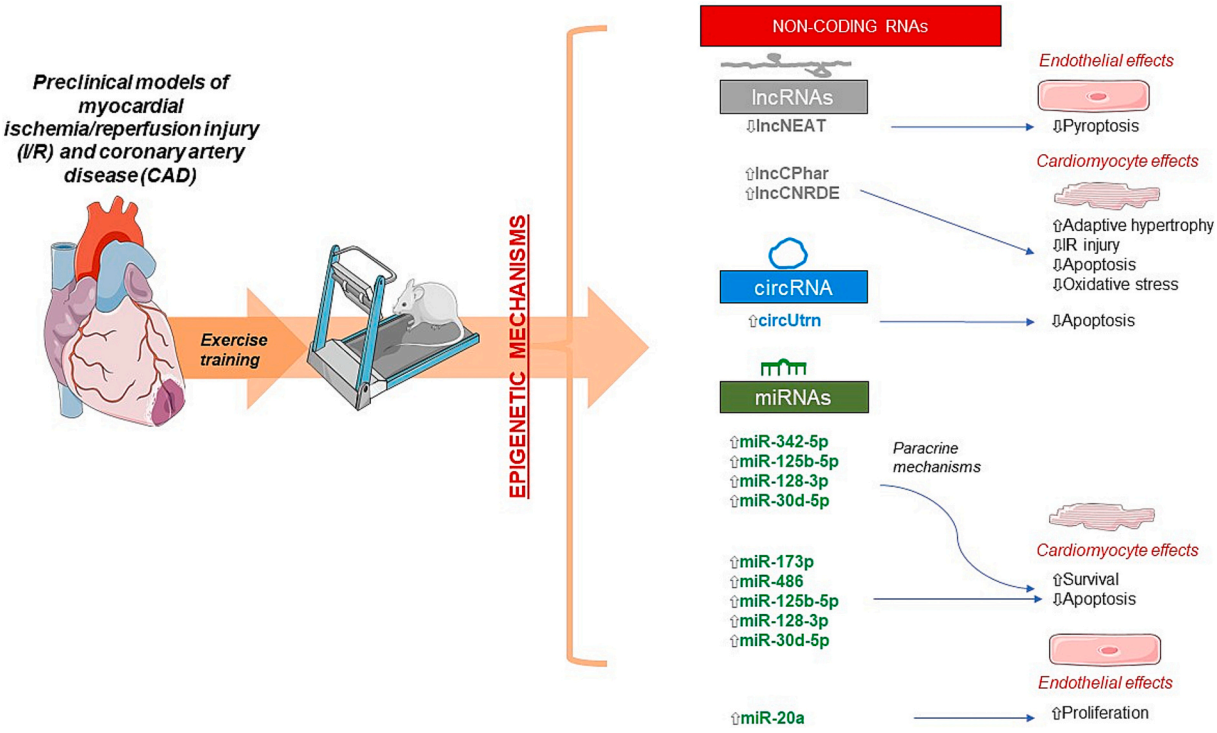

Fig. 3. Modulation of epigenetic mechanisms by exercise training in preclinical models of ischemia/reperfusion (I/R) injury or coronary artery disease (CAD). Exercise increases levels of several microRNAs (miRNAs). miRNAs exerts protective effects in both cardiomyocytes and endothelial cells. Exercise also modulates long non-coding RNAs and circularRNAs, which in turn contribute to reduces I/R injury. See text for further details. This figure was generated in part using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

mouse fed with a high-fat diet (HFD), the long non-coding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1) was found to be downregulated by exercise in atherosclerotic lesions [113]. The reduced expression of NEAT1 leads to a decrease in endothelial pyroptosis, which prevents the progression of atherosclerosis. Circulating levels of NEAT1 were found to be lower in peripheral plasma samples from patients with coronary heart disease (CHD) who exercise regularly [113]. It would be interesting to evaluate the cardiac-specific role of NEAT1 in future studies. CPhar is another lncRNA that was found upregulated in the heart of mice undergoing swimming, promoting physiological hypertrophy. CPhar overexpression reduces myocardial I/R injury. At the molecular level, CPhar reduces the expression of ATF7, a transcription factor that negatively regulates cell proliferation. However, whether the protective effects of exercise in models of I/R injury are reduced in the presence of CPhar inhibition has not been investigated yet [114].

Long-term exercise in mice upregulates the expression of LncRNA colorectal neoplasia differentially expressed (CRNDE) in exosomes and CRNDE inhibition abrogates the protective effects of exercise in response to I/R in mice. At the molecular level, CRNDE inhibition leads to the reduction of Nrf2 via miR-489-3p, increasing oxidative stress and apoptosis [115].

Another recent study also found that swimming exercise reduces I/R in mice and pathological remodelling through the upregulation of the circRNA circUtrn in cardiomyocytes. circUtrn interacts with protein phosphatase 5 (PP5) and promotes its degradation via the ubiquitin system [116]. The reduced activity of PP5 activates the MAPK/ERK signaling, which in turn reduces cardiomyocyte apoptosis.

Finally, plasma samples of patients undergoing cardiac surgery on cardiopulmonary bypass show postoperative changes in DNA methylation, which are associated with postoperative atrial fibrillation (POAF), a common consequence of cardiac surgery. Loci with changes in DNA methylation are found within genes regulating endoplasmic reticulum stress, apoptosis, and glucose metabolism [117].

5. Cardiac aging

During aging, the heart undergoes an inevitable structural and functional decline, leading to an increased risk of HF and mortality [118]. The aged heart is characterized by telomere shortening, the activation of pro-senescence pathways, and increased oxidative stress and inflammation. In contrast, adaptive mechanisms, such as autophagy and regeneration resulted impaired [118]. Epigenetic alterations represent a hallmark of aging and several patterns of DNA methylation, histone modifications, and different non-coding RNAs have been proposed to contribute to cardiac aging in both animal models and older individuals [119,120]. Exercise slows cardiac aging, through the reduction of senescence factors, inflammation, and oxidative stress, and the improvement of mitochondrial health and autophagy [118,121–125]. To the best of our knowledge, few studies investigated the effects of exercise on epigenetic signatures in older individuals. Older men undergoing acute exercise show a differential expression of circulating miRNA involved in cardiac hypertrophy and remodelling, compared to sedentary individuals [126]. However, further mechanistic studies to be performed in aged animal models should clarify which epigenetic mechanism mediates the cardioprotective effects of exercise.

6. Conclusions

Exercise is recognized as a healthy lifestyle modification for preventing CVD risk factors and represents the cornerstone of CR for patients with cardiac diseases. The fundamental role of exercise training in reducing CV mortality and re-hospitalization in patients with HF or CAD and subjects undergoing cardiac surgery for valve replacement or CABG is well known and described. The importance of adopting standardized exercise programs regarding the type of exercise, frequency, and

intensity to achieve maximal beneficial cardiac effects is also well-known and described.

Moreover, CR programs should assist CV patients in developing the skills to successfully self-manage their conditions, improve exercise capacity and QoL, and complement the impact of drugs and devices in reducing hospitalizations. CR programs confer cardiac protection by suppressing inflammation and activating specific adaptive mechanisms. Indeed, recent experimental evidence demonstrates that exercise has beneficial effects by acting on specific signals in both cardiomyocytes and non-cardiomyocytes, particularly on epigenetic mechanisms that promote cardiac regeneration and growth and inhibit apoptotic and inflammatory signals. Exercise rescues the level of specific miRNAs and lncRNAs modulated by cardiac stress (Table 1). Remarkably, the modulation of specific miRNAs or lncRNAs was also observed in the serum of patients undergoing CR or in exercise-trained healthy subjects, perfectly recapitulating preclinical data [8,109,113]; precisely, exercise training confers direct protection against myocardial I/R injury. Indeed, long-term exercise-derived circulating exosomes protect the heart against myocardial I/R injury via exosomal miR-342-5p[8]; moreover, miR-17-3p contributes to exercise-induced cardiac growth and protects against adverse ventricular remodelling. Consequently, these miRNAs may represent novel therapeutic targets to promote functional recovery after cardiac injury, and non-coding RNAs could be predictive biomarkers for CR success in patients.

7. Future perspectives

The role of biomarkers in CR is widely discussed in the literature, and there is considerable evidence that exercise modifies inflammatory markers [127–130]. However, there is little evidence about using ncRNA as biomarkers for patients' stratification, prognosis, and follow-up during rehabilitation programs [131]. Medical research and technology are exploring biomarkers to enhance risk stratification [132,133], optimize treatment strategies [134–136], and tailor rehabilitation programs to individual needs.

Identifying novel biomarkers associated with CR may lay the foundation for effective biomarker-guided CR, providing the molecular basis for developing new approaches or using current pharmacological therapies to improve functional recovery. Based on biomarkers, novel pharmacological therapies that mimic some of the benefits of exercise may be developed [137]. In this regard, the inhibition of miR-132 by CDR132L, a specific antisense oligonucleotide, was reported to improve cardiac function in patients on standard-of-care therapy for chronic ischaemic HF [138]. At the molecular level, the inhibition of miR-132 was reported to improve FOXO3-induced anti-hypertrophic and pro-autophagic effects in cardiomyocytes [139]. It should be interesting to test whether CR can rescue miR-132 levels in patients.

Gene therapy is one of the most promising ways to achieve this goal. Indeed, cardiac-specific gene therapy is already possible [140]; therefore, the hypothesis of 'delivering' some aspects of the cardiac benefits of exercise through pharmacological approaches can now be improved. Moreover, another way to translate the basic science findings into exercise-mimicking therapies would be through the modulation of critical molecular targets of exercise adaptations. For instance, high doses of certain natural extracts, such as resveratrol, can improve endurance [141,142].

Conversely, other intrapersonal, interpersonal, clinical, logistical, health system and CR program-related factors affect participation and

Table 1
Direct or indirect evidence of modulation of non-coding RNAs by exercise training in different preclinical models of cardiac disease and mechanism of cardioprotection.

Exercise	Experimental model	Non-coding RNA	Target	Cardiac effects	PMID Reference
8 weeks – Running exercise 24 h post-MI	Mice/MI	↑miR-222	↓ HIPK1	↑cardiac regeneration	29695718
8 weeks – Running exercise 1-week post-MI			↓ HIPK2	↓ cardiomyocyte apoptosis	34837851
4 weeks- swim training 24 h post MI	Mice/MI	↑miR-1192	↓ caspase 3 ↑Bcl-2 ↓ Bax ↓ TGFβ-1	↓ cardiomyocyte apoptosis	31733833
Voluntary running for 8 weeks	Mice/baseline	↓ lncExACT1	↓ DCHS2 ↑yap ↓ MST1/MST2	lncExACT1 inhibition protects the heart against adverse remodelling	35114812
Moderate-running for 4 weeks	Rats/MI	↑ lncH19 ↓ lncMIAT ↑lncGAS 5	Not investigated	↓fibrosis ↓apoptosis	32935227
Aerobic exercise training over an 8-week four weeks post-surgery	Rats/MI	↓ lncMALAT 1	↑miR-150 ↑PI3K/AKT	↓apoptosis ↑autophagy	33708967
Swimming exercise for 1 week after surgery	Mice/PO	↑ miR-574-3p	↓ IL-6	↓ inflammation	38410978
Intensive swim exercise protocol	Mice/baseline	↑ miR-30d	Not investigated	↓fibrosis miR-30d inhibition accelerates heart failure in mice in response to TAC	32418505
Exercise hypertrophic preconditioning [EHP]	Mice/PO	↑lncMhrt779	↓ p-Akt ↓ p-GSK3β	↑antihypertrophic effects	33757294
4 weeks- swim training before I/R	Rats/myocardial I/R injury	↑miR-3525p	↑p-Akt ↓ caspase 9 ↓ JNK-2	↓ cardiomyocyte apoptosis ↓ infarct size	30879399
3 weeks – Swim training	Mice/baseline	↑miR-17-3p	↓ TIMP-3	miR-17-3p mimic administration reduces I/R injury	28255358
4 weeks - swim training	Mice/IR injury	↑miR-125b-5p ↑miR-128-3p ↑miR-30d-5p	↓ MAPK	↓ apoptosis	35387487
3 weeks- swim training before I/R	Mice/IR injury	↑miR-486	↓ PTEN ↓ FOXO1	↓ cardiomyocyte apoptosis ↓ infarct size	35077859
Long term exercise	Mice/IR injury	↑lncCRNDE	↑ Nrf-2 ↓ miR-489-3p	↓ apoptosis ↓ oxidative stress	37940009
3 weeks-swim training	Mice/baseline	↑lncCPhar	↓ ATF7	CPhar overexpression in vivo reduces I/R injury	34015936
4 weeks- swim training	Mice/IR injury	↑circRNA circUtrn	↓ PEG5 ↑MAPK/ERK	↓ pathological remodelling ↓ apoptosis	37897547

adherence [143].

Consequently, there is still suboptimal uptake and inequities in access to CR, and home and telehealth-based interventions are increasingly used as alternatives to traditional center-based rehabilitation programs [144–147] to overcome access, especially in rural areas [148]. Specifically, technological developments can potentially implement other appropriate options to alleviate the limitations of conventional CR interventions by providing individual real-time assistance to patients in their environment [146].

Simultaneously, additional research is needed to extend access to exercise-based therapy for HFpEF, HFmrEF, or subgroups often underrepresented in trials: women, ethnic minorities, and those with multimorbidity.

Furthermore, few observational studies reported that cardiac surgery also influences epigenetic mechanisms. In this regard, adult individuals undergoing heart surgery exhibit elevated serum levels of histone 3 (tH3) that persist until 3 months later. Circulating levels of H3K4me3 and H3K27ac, two histone modifications, are also modulated by cardiac surgery. tH3 levels correlate with post-operative features, such as the length of stay in the hospital and with immune activation [149].

Further studies should investigate whether circulating levels of tH3 and DNA methylation may be considered prognostic biomarkers of CR in patients undergoing cardiac surgery. It should also be tested whether CR can faster rescue post-operative circulating levels of histone and DNA methylation to pre-operative levels.

Finally, the effects of exercise should be tested in relevant and translational preclinical models, such as in large animals (i.e., porcine model). In all these settings, understanding non-coding RNAs and their associated targets in patients undergoing CR can support the identification of the specific phenotype and the development of personalized patient-specific CR protocols.

CRediT authorship contribution statement

Valeria Visco: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Conceptualization. **Maurizio Forte:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Data curation, Conceptualization. **Francesco Giallauria:** Writing – original draft, Conceptualization. **Luca D'Ambrosio:** Writing – original draft, Conceptualization. **Mara Piccoli:** Writing – original draft, Conceptualization. **Gabriele G. Schiattarella:** Writing – original draft, Conceptualization. **Costantino Mancusi:** Writing – original draft, Conceptualization. **Nadia Salerno:** Writing – original draft, Conceptualization. **Arturo Cesaro:** Writing – original draft, Conceptualization. **Marco Alfonso Perrone:** Writing – original draft, Conceptualization. **Carmine Izzo:** Writing – original draft, Conceptualization. **Francesco S. Loffredo:** Writing – original draft, Conceptualization. **Michele Bellino:** Writing – original draft, Conceptualization. **Edoardo Bertero:** Writing – original draft, Conceptualization. **Nicola De Luca:** Writing – original draft, Conceptualization. **Kalliopi Pilichou:** Writing – original draft, Conceptualization. **Paolo Calabrò:** Writing – original draft, Conceptualization. **Girolamo Manno:** Writing – original draft, Conceptualization. **Elena De Falco:** Writing – original draft, Conceptualization. **Albino Carrizzo:** Writing – original draft, Conceptualization. **Valentina Valenti:** Writing – original draft, Conceptualization. **Silvia Castelletti:** Writing – original draft, Conceptualization. **Luigi Spadafora:** Writing – original draft, Conceptualization. **Nidal Tourkmani:** Writing – original draft, Conceptualization. **Antonello D'Andrea:** Writing – original draft, Conceptualization. **Mario Pacileo:** Writing – original draft, Conceptualization. **Marco Bernardi:** Writing – original draft, Conceptualization. **Alessandro Maloberti:** Writing – original draft. **Beatrice Simeone:** Writing – original draft, Conceptualization. **Gianmarco Sarto:** Writing – original draft, Conceptualization. **Giacomo Frati:** Writing – original draft, Conceptualization. **Cinzia Perrino:** Writing – original draft, Conceptualization. **Roberto Pedrinelli:** Writing – review & editing. **Pasquale Perrone Filardi:** Writing – review & editing. **Carmine Vecchione:** Writing – original draft, Conceptualization. **Sebastiano Sciarretta:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Data curation, Conceptualization. **Michele Ciccarelli:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Data curation, Conceptualization.

References

[1] M. Ciccarelli, F. Giallauria, A. Carrizzo, V. Visco, A. Silverio, A. Cesaro, et al., Artificial intelligence in cardiovascular prevention: new ways will open new doors, J. Cardiovasc. Med. (Hagerstown) 24 (Suppl. 2) (2023) e106–e115.

[2] V. Visco, G.J. Ferruzzi, F. Nicastro, N. Virtuoso, A. Carrizzo, G. Galasso, et al., Artificial intelligence as a business partner in cardiovascular precision medicine: an emerging approach for disease detection and treatment optimization, Curr. Med. Chem. 28 (32) (2021) 6569–6590.

[3] R.S. Taylor, H.M. Dalal, A.D. Zwisler, Cardiac rehabilitation for heart failure: 'Cinderella' or evidence-based pillar of care? Eur. Heart J. 44 (17) (2023) 1511–1518.

[4] J. Redfern, R. Gallagher, A. O'Neil, S.L. Grace, A. Bauman, G. Jennings, et al., Historical context of cardiac rehabilitation: learning from the past to move to the future, Front. Cardiovasc. Med. 9 (2022) 842567.

[5] K. Goel, Q.R. Pack, B. Lahr, K.L. Greason, F. Lopez-Jimenez, R.W. Squires, et al., Cardiac rehabilitation is associated with reduced long-term mortality in patients undergoing combined heart valve and CABG surgery, Eur. J. Prev. Cardiol. 22 (2) (2015) 159–168.

[6] G.J. Balady, P.A. Ades, V.A. Bittner, B.A. Franklin, N.F. Gordon, R.J. Thomas, et al., Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association, Circulation 124 (25) (2011) 2951–2960.

[7] F. Giallauria, T. Strisciuglio, G. Cuomo, A. Di Lorenzo, A. D'Angelo, M. Volpicelli, et al., Exercise training: the holistic approach in cardiovascular prevention, High Blood Press Cardiovasc. Prev. 28 (6) (2021) 561–577.

[8] Z. Hou, X. Qin, Y. Hu, X. Zhang, G. Li, J. Wu, et al., Longterm exercise-derived Exosomal miR-342-5p: a novel exerkine for cardioprotection, Circ. Res. 124 (9) (2019) 1386–1400.

[9] H. Lin, Y. Zhu, C. Zheng, D. Hu, S. Ma, L. Chen, et al., Antihypertrophic memory after regression of exercise-induced physiological myocardial hypertrophy is mediated by the Long noncoding RNA Mhrt779, Circulation 143 (23) (2021) 2277–2292.

[10] Y. Bei, D. Lu, C. Bar, S. Chatterjee, A. Costa, I. Riedel, et al., miR-486 attenuates cardiac ischemia/reperfusion injury and mediates the beneficial effect of exercise for myocardial protection, Mol. Ther. 30 (4) (2022) 1675–1691.

[11] A. Vujic, C. Lerchenmuller, T.D. Wu, C. Guillermier, C.P. Rabolli, E. Gonzalez, et al., Exercise induces new cardiomyocyte generation in the adult mammalian heart, Nat. Commun. 9 (1) (2018) 1659.

[12] W. Zhang, M. Song, J. Qu, G.H. Liu, Epigenetic modifications in cardiovascular aging and diseases, Circ. Res. 123 (7) (2018) 773–786.

[13] R. Papait, S. Serio, G. Condorelli, Role of the epigenome in heart failure, Physiol. Rev. 100 (4) (2020) 1753–1777.

[14] A.B. Gevaert, N. Wood, J.R.A. Boen, C.H. Davos, D. Hansen, H. Hanssen, et al., Epigenetics in the primary and secondary prevention of cardiovascular disease: influence of exercise and nutrition, Eur. J. Prev. Cardiol. 29 (17) (2022) 2183–2199.

[15] R. Jaenisch, A. Bird, Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals, Nat. Genet. 33 (Suppl) (2003) 245–254.

[16] P. van der Harst, L.J. de Windt, J.C. Chambers, Translational perspective on epigenetics in cardiovascular disease, J. Am. Coll. Cardiol. 70 (5) (2017) 590–606.

[17] J.C. Rice, S.D. Briggs, B. Ueberheide, C.M. Barber, J. Shabanowitz, D.F. Hunt, et al., Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains, Mol. Cell 12 (6) (2003) 1591–1598.

[18] R. Marmorstein, S.Y. Roth, Histone acetyltransferases: function, structure, and catalysis, Curr. Opin. Genet. Dev. 11 (2) (2001) 155–161.

[19] K. Karmodiya, A.R. Krebs, M. Oulad-Abdelghani, H. Kimura, L. Tora, H3K9 and H3K14 acetylation co-occur at many gene regulatory elements, while H3K14ac marks a subset of inactive inducible promoters in mouse embryonic stem cells, BMC Genomics 13 (2012) 424.

[20] J. Lu, S. Qian, Z. Sun, Targeting histone deacetylase in cardiac diseases, Front. Physiol. 15 (2024) 1405569.

[21] C.L. Zhang, T.A. McKinsey, S. Chang, C.L. Antos, J.A. Hill, E.N. Olson, Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy, Cell 110 (4) (2002) 479–488.

[22] R. Margueron, D. Reinberg, Chromatin structure and the inheritance of epigenetic information, Nat. Rev. Genet. 11 (4) (2010) 285–296.

[23] M. Jain, M.F. Jantsch, K. Licht, The Editor's I on disease development, Trends Genet. 35 (12) (2019) 903–913.

[24] M. Jain, T.D. Mann, M. Stulic, S.P. Rao, A. Kirsch, D. Pullirsch, et al., RNA editing of Filamin a pre-mRNA regulates vascular contraction and diastolic blood pressure, EMBO J. 37 (19) (2018).

[25] K. Stellos, A. Gatsiou, K. Stamatelopoulos, L. Perisic Matic, D. John, F.F. Lunella, et al., Adenosine-to-inosine RNA editing controls cathepsin S expression in

atherosclerosis by enabling HuR-mediated post-transcriptional regulation, Nat. Med. 22 (10) (2016) 1140–1150.
[26] S. Costantino, P. Libby, R. Kishore, J.C. Tardif, A. El-Osta, F. Paneni, Epigenetics and precision medicine in cardiovascular patients: from basic concepts to the clinical arena, Eur. Heart J. 39 (47) (2018) 4150–4158.
[27] P. Kapranov, J. Cheng, S. Dike, D.A. Nix, R. Duttagupta, A.T. Willingham, et al., RNA maps reveal new RNA classes and a possible function for pervasive transcription, Science 316 (5830) (2007) 1484–1488.
[28] S.U. Schmitz, P. Grote, B.G. Herrmann, Mechanisms of long noncoding RNA function in development and disease, Cell. Mol. Life Sci. 73 (13) (2016) 2491–2509.
[29] W. Gao, M. Zhu, H. Wang, S. Zhao, D. Zhao, Y. Yang, et al., Association of polymorphisms in long non-coding RNA H19 with coronary artery disease risk in a Chinese population, Mutat. Res. 772 (2015) 15–22.
[30] N. Ishii, K. Ozaki, H. Sato, H. Mizuno, S. Susumu, A. Takahashi, et al., Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction, J. Hum. Genet. 51 (12) (2006) 1087–1099.
[31] J.D. Mably, D.Z. Wang, Long non-coding RNAs in cardiac hypertrophy and heart failure: functions, mechanisms and clinical prospects, Nat. Rev. Cardiol. 21 (5) (2024) 326–345.
[32] S. Das, R. Shah, S. Dimmeler, J.E. Freedman, C. Holley, J.M. Lee, et al., Noncoding RNAs in cardiovascular disease: current knowledge, tools and Technologies for Investigation, and future directions: a scientific statement from the American Heart Association, Circ. Genom. Precis. Med. 13 (4) (2020) e000062.
[33] A. Bibi, M. Bartekova, S. Gandhi, S. Greco, A. Madè, M. Sarkar, et al., CardioRNA COST Action CA17129 and AtheroNET COST Action CA21153. Circular RNA regulatory role in pathological cardiac remodelling, Br. J. Pharmacol. 182 (2) (2025) 316–339, https://doi.org/10.1111/bph.16434. Epub 2024 Jun 3. PMID: 38830749.
[34] A.A. Baccarelli, J. Ordovas, Epigenetics of early cardiometabolic disease: mechanisms and precision medicine, Circ. Res. 132 (12) (2023) 1648–1662.
[35] V. Visco, C. Esposito, P. Vitillo, C. Vecchione, M. Ciccarelli, It is easy to see, but it is better to foresee: a case report on the favourable alliance between CardioMEMS and levosimendan, Eur. Heart J. Case Rep. 4 (4) (2020) 1–5.
[36] V. Visco, C. Esposito, M. Manzo, A. Fiorentino, G. Galasso, C. Vecchione, et al., A multistep approach to Deal with advanced heart failure: a case report on the positive effect of cardiac contractility modulation therapy on pulmonary pressure measured by CardioMEMS, Front. Cardiovasc. Med. 9 (2022) 874433.
[37] A. Pandey, A. Parashar, D. Kumbhani, S. Agarwal, J. Garg, D. Kitzman, et al., Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials, Circ. Heart Fail. 8 (1) (2015) 33–40.
[38] R.S. Taylor, S. Walker, N.A. Smart, M.F. Piepoli, F.C. Warren, O. Ciani, et al., Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials, Eur. J. Heart Fail. 20 (12) (2018) 1735–1743.
[39] R.S. Taylor, S. Walker, N.A. Smart, M.F. Piepoli, F.C. Warren, O. Ciani, et al., Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis, J. Am. Coll. Cardiol. 73 (12) (2019) 1430–1443.
[40] V. Visco, I. Radano, A. Campanile, A. Ravera, A. Silverio, D. Masarone, et al., Predictors of sacubitril/valsartan high dose tolerability in a real world population with HFrEF, ESC Heart Fail 9 (5) (2022) 2909–2917.
[41] C.M. O'Connor, D.J. Whellan, K.L. Lee, S.J. Keteyian, L.S. Cooper, S.J. Ellis, et al., Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial, JAMA 301 (14) (2009) 1439–1450.
[42] K.E. Flynn, I.L. Pina, D.J. Whellan, L. Lin, J.A. Blumenthal, S.J. Ellis, et al., Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial, JAMA 301 (14) (2009) 1451–1459.
[43] L.B. Cooper, R.J. Mentz, J.L. Sun, P.J. Schulte, J.L. Fleg, L.S. Cooper, et al., Psychosocial factors, exercise adherence, and outcomes in heart failure patients: insights from heart failure: a controlled trial investigating outcomes of exercise training (HF-ACTION), Circ. Heart Fail. 8 (6) (2015) 1044–1051.
[44] B. Bozkurt, G.C. Fonarow, L.R. Goldberg, M. Guglin, R.A. Josephson, D. E. Forman, et al., Cardiac rehabilitation for patients with heart failure: JACC expert panel, J. Am. Coll. Cardiol. 77 (11) (2021) 1454–1469.
[45] A. Pelliccia, S. Sharma, S. Gati, M. Back, M. Borjesson, S. Caselli, et al., 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease, Eur. Heart J. 42 (1) (2021) 17–96.
[46] J. Scherr, B. Wolfarth, J.W. Christle, A. Pressler, S. Wagenpfeil, M. Halle, Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity, Eur. J. Appl. Physiol. 113 (1) (2013) 147–155.
[47] U. Corra, P.G. Agostoni, S.D. Anker, A.J.S. Coats, M.G. Crespo Leiro, R.A. de Boer, et al., Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the committee on exercise physiology and training of the heart failure Association of the European Society of cardiology, Eur. J. Heart Fail. 20 (1) (2018) 3–15.
[48] A. Campanile, V. Visco, S. De Carlo, G.J. Ferruzzi, C. Mancusi, C. Izzo, et al., Sacubitril/valsartan vs. standard medical therapy on exercise capacity in HFrEF patients, Life 13 (5) (2023).
[49] Z. Wang, J. Yan, S. Meng, J. Li, Y. Yu, T. Zhang, et al., Reliability and validity of sit-to-stand test protocols in patients with coronary artery disease, Front. Cardiovasc. Med. 9 (2022) 841453.
[50] M. Meriem, J. Cherif, S. Toujani, Y. Ouahchi, A.B. Hmida, M. Beji, Sit-to-stand test and 6-min walking test correlation in patients with chronic obstructive pulmonary disease, Ann. Thorac. Med. 10 (4) (2015) 269–273.
[51] M.M. Gross, P.J. Stevenson, S.L. Charette, G. Pyka, R. Marcus, Effect of muscle strength and movement speed on the biomechanics of rising from a chair in healthy elderly and young women, Gait Posture 8 (3) (1998) 175–185.
[52] L. Long, I.R. Mordi, C. Bridges, V.A. Sagar, E.J. Davies, A.J. Coats, et al., Exercise-based cardiac rehabilitation for adults with heart failure, Cochrane Database Syst. Rev. 1 (1) (2019) CD003331.
[53] F.L.J. Visseren, F. Mach, Y.M. Smulders, D. Carballo, K.C. Koskinas, M. Back, et al., 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice, Eur. Heart J. 42 (34) (2021) 3227–3337.
[54] D. Hansen, P. Dendale, K. Coninx, L. Vanhees, M.F. Piepoli, J. Niebauer, et al., The European Association of Preventive Cardiology Exercise Prescription in everyday practice and rehabilitative training (EXPERT) tool: a digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology, Eur. J. Prev. Cardiol. 24 (10) (2017) 1017–1031.
[55] B. Abell, P. Glasziou, T. Hoffmann, The contribution of individual exercise training components to clinical outcomes in randomised controlled trials of cardiac rehabilitation: a systematic review and meta-regression, Sports Med. Open 3 (1) (2017) 19.
[56] K. Liu, W. Ju, S. Ouyang, Z. Liu, F. He, J. Hao, et al., Exercise training ameliorates myocardial phenotypes in heart failure with preserved ejection fraction by changing N6-methyladenosine modification in mice model, Front. Cell Dev. Biol. 10 (2022) 954769.
[57] J.D. Roh, N. Houstis, A. Yu, B. Chang, A. Yeri, H. Li, et al., Exercise training reverses cardiac aging phenotypes associated with heart failure with preserved ejection fraction in male mice, Aging Cell 19 (6) (2020) e13159.
[58] M. Valero-Munoz, W. Backman, F. Sam, Murine models of heart failure with preserved ejection fraction: a "fishing expedition", JACC Basic Transl. Sci. 2 (6) (2017) 770–789.
[59] T. Fernandes, F.C. Magalhaes, F.R. Roque, M.I. Phillips, E.M. Oliveira, Exercise training prevents the microvascular rarefaction in hypertension balancing angiogenic and apoptotic factors: role of microRNAs-16, −21, and −126, Hypertension 59 (2) (2012) 513–520.
[60] Y. Masoumi-Ardakani, H. Najafipour, H.R. Nasri, S. Aminizadeh, S. Jafari, Z. Safi, Moderate endurance training and MitoQ improve cardiovascular function, oxidative stress, and inflammation in hypertensive individuals: the role of miR-21 and miR-222: a randomized, double-blind, Clin. Trial. Cell J. 24 (10) (2022) 577–585.
[61] M. Fernandez-Sanjurjo, P. Pinto-Hernandez, A. Davalos, A.E. Diaz-Martinez, R. Martin-Hernandez, J. Castilla-Silgado, et al., Next-generation sequencing reveals that miR-16-5p, miR-19a-3p, miR-451a, and miR-25-3p cargo in plasma extracellular vesicles differentiates sedentary young males from athletes, Eur. J. Sport Sci. 24 (6) (2024) 766–776.
[62] X. Liu, J. Xiao, H. Zhu, X. Wei, C. Platt, F. Damilano, et al., miR-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac remodeling, Cell Metab. 21 (4) (2015) 584–595.
[63] A.L. Baggish, A. Hale, R.B. Weiner, G.D. Lewis, D. Systrom, F. Wang, et al., Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training, J. Physiol. 589 (Pt 16) (2011) 3983–3994.
[64] L. Wang, Y. Lv, G. Li, J. Xiao, MicroRNAs in heart and circulation during physical exercise, J. Sport Health Sci. 7 (4) (2018) 433–441.
[65] Q. Zhou, J. Deng, J. Yao, J. Song, D. Meng, Y. Zhu, et al., Exercise downregulates HIPK2 and HIPK2 inhibition protects against myocardial infarction, EBioMedicine 74 (2021) 103713.
[66] Y. Wang, M.M. Tian, C.J. Mi, K.L. Chen, Y.C. Ji, L. Wang, et al., Exercise protects the heart against myocardial infarction through upregulation of miR-1192, Biochem. Biophys. Res. Commun. 521 (4) (2020) 1061–1069.
[67] N. Rolim, K. Skardal, M. Hoydal, M.M. Sousa, V. Malmo, G. Kaurstad, et al., Aerobic interval training reduces inducible ventricular arrhythmias in diabetic mice after myocardial infarction, Basic Res. Cardiol. 110 (4) (2015) 44.
[68] J.K. Lew, J.T. Pearson, E. Saw, H. Tsuchimochi, M. Wei, N. Ghosh, et al., Exercise regulates MicroRNAs to preserve coronary and cardiac function in the diabetic heart, Circ. Res. 127 (11) (2020) 1384–1400.
[69] A. Hsu, S.J. Chen, Y.S. Chang, H.C. Chen, P.H. Chu, Systemic approach to identify serum microRNAs as potential biomarkers for acute myocardial infarction, Biomed. Res. Int. 2014 (2014) 418628.
[70] Y. Ma, H. Liu, Y. Wang, J. Xuan, X. Gao, H. Ding, et al., Roles of physical exercise-induced MiR-126 in cardiovascular health of type 2 diabetes, Diabetol. Metab. Syndr. 14 (1) (2022) 169.
[71] R. Yamada, S. Okumura, Y. Kono, A. Miyazaki, Y. Niwa, T. Ito, et al., Effect of cardiac rehabilitation on circulating microRNA expression in heart failure: a preliminary study, Fujita Med. J. 7 (3) (2021) 76–82.
[72] S.J. Farsangi, F. Rostamzadeh, M. Sheikholeslami, E. Jafari, M. Karimzadeh, Modulation of the expression of Long non-coding RNAs H19, GAS5, and MIAT by endurance exercise in the hearts of rats with myocardial infarction, Cardiovasc. Toxicol. 21 (2) (2021) 162–168.
[73] L. Hu, Y.N. Xu, Q. Wang, M.J. Liu, P. Zhang, L.T. Zhao, et al., Aerobic exercise improves cardiac function in rats with chronic heart failure through inhibition of the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), Ann. Transl. Med. 9 (4) (2021) 340.
[74] E.A. Toraih, A. El-Wazir, S.A. Alghamdi, A.S. Alhazmi, M. El-Wazir, M.M. Abdel-Daim, et al., Association of long non-coding RNA MIAT and MALAT1 expression profiles in peripheral blood of coronary artery disease patients with previous cardiac events, Genet. Mol. Biol. 42 (3) (2019) 509–518.

[75] W. Zhao, Y. Yin, H. Cao, Y. Wang, Exercise improves endothelial function via the lncRNA MALAT1/miR-320a Axis in obese children and adolescents, Cardiol. Res. Pract. 2021 (2021) 8840698.
[76] X. Wu, L. Wang, K. Wang, J. Li, R. Chen, X. Wu, et al., ADAR2 increases in exercised heart and protects against myocardial infarction and doxorubicin-induced cardiotoxicity, Mol. Ther. 30 (1) (2022) 400–414.
[77] H. Jiang, D. Jia, B. Zhang, W. Yang, Z. Dong, X. Sun, et al., Exercise improves cardiac function and glucose metabolism in mice with experimental myocardial infarction through inhibiting HDAC4 and upregulating GLUT1 expression, Basic Res. Cardiol. 115 (3) (2020) 28.
[78] A. Care, D. Catalucci, F. Felicetti, D. Bonci, A. Addario, P. Gallo, et al., MicroRNA-133 controls cardiac hypertrophy, Nat. Med. 13 (5) (2007) 613–618.
[79] Q.Y. Chen, Y.N. Jiang, X. Guan, F.F. Ren, S.J. Wu, M.P. Chu, et al., Aerobic exercise attenuates pressure overload-induced myocardial remodeling and myocardial inflammation via upregulating miR-574-3p in mice, Circ. Heart Fail. 17 (3) (2024) e010569.
[80] C. Lerchenmuller, C.P. Rabolli, A. Yeri, R. Kitchen, A.M. Salvador, L.X. Liu, et al., CITED4 protects against adverse remodeling in response to physiological and pathological stress, Circ. Res. 127 (5) (2020) 631–646.
[81] Y. Huang, Y. Zhang, W. Nong, B. Lan, D. Zhang, Functional significance of cardiac rehabilitation-regulated expression of circulating MicroRNA-423-5p in hypertensive patients with heart failure with a moderately reduced ejection fraction, Anatol. J. Cardiol. 26 (5) (2022) 366–372.
[82] L.A. Goldraich, N.C. Martinelli, U. Matte, C. Cohen, M. Andrades, M. Pimentel, et al., Transcoronary gradient of plasma microRNA 423-5p in heart failure: evidence of altered myocardial expression, Biomarkers 19 (2) (2014) 135–141.
[83] O. Tutarel, S. Dangwal, J. Bretthauer, M. Westhoff-Bleck, P. Roentgen, S. D. Anker, et al., Circulating miR-423_5p fails as a biomarker for systemic ventricular function in adults after atrial repair for transposition of the great arteries, Int. J. Cardiol. 167 (1) (2013) 63–66.
[84] A.J. Tijsen, E.E. Creemers, P.D. Moerland, L.J. de Windt, A.C. van der Wal, W. E. Kok, et al., MiR423-5p as a circulating biomarker for heart failure, Circ. Res. 106 (6) (2010) 1035–1039.
[85] H. Li, L.E. Trager, X. Liu, M.H. Hastings, C. Xiao, J. Guerra, et al., lncExACT1 and DCHS2 regulate physiological and pathological cardiac growth, Circulation 145 (16) (2022) 1218–1233.
[86] L.H. Lehmann, Z.H. Jebessa, M.M. Kreusser, A. Horsch, T. He, M. Kronlage, et al., A proteolytic fragment of histone deacetylase 4 protects the heart from failure by regulating the hexosamine biosynthetic pathway, Nat. Med. 24 (1) (2018) 62–72.
[87] B. Butts, J. Butler, S.B. Dunbar, E. Corwin, R.A. Gary, Effects of exercise on ASC methylation and IL-1 cytokines in heart failure, Med. Sci. Sports Exerc. 50 (9) (2018) 1757–1766.
[88] G. Wu, X. Zhang, F. Gao, The epigenetic landscape of exercise in cardiac health and disease, J. Sport Health Sci. 10 (6) (2021) 648–659.
[89] M.R. Sailani, J.F. Halling, H.D. Moller, H. Lee, P. Plomgaard, H. Pilegaard, et al., Lifelong physical activity is associated with promoter hypomethylation of genes involved in metabolism, myogenesis, contractile properties and oxidative stress resistance in aged human skeletal muscle, Sci. Rep. 9 (1) (2019) 3272.
[90] S.X. Liu, F. Zheng, K.L. Xie, M.R. Xie, L.J. Jiang, Y. Cai, Exercise reduces insulin resistance in type 2 diabetes mellitus via mediating the lncRNA MALAT1/MicroRNA-382-3p/Resistin Axis, Mol. Ther. Nucleic Acids 18 (2019) 34–44.
[91] A.B. Gevaert, I. Witvrouwen, A.H. Van Craenenbroeck, S.J. Van Laere, J.R. A. Boen, C.M. Van de Heyning, et al., miR-181c level predicts response to exercise training in patients with heart failure and preserved ejection fraction: an analysis of the OptimEx-Clin trial, Eur. J. Prev. Cardiol. 28 (15) (2021) 1722–1733.
[92] D. Jin, X.Y. Yang, J.S. Wang, MicroRNA-126 level increases during exercise rehabilitation of heart failure with a preserved ejection fraction, Int. J. Gen. Med. 14 (2021) 3397–3404.
[93] S.S. Jankauskas, P. Mone, R. Avvisato, F. Varzideh, S. De Gennaro, L. Salemme, et al., miR-181c targets Parkin and SMAD7 in human cardiac fibroblasts: validation of differential microRNA expression in patients with diabetes and heart failure with preserved ejection fraction, Mech. Ageing Dev. 212 (2023) 111818.
[94] X. Zheng, Y. Zheng, J. Ma, M. Zhang, Y. Zhang, X. Liu, et al., Effect of exercise-based cardiac rehabilitation on anxiety and depression in patients with myocardial infarction: a systematic review and meta-analysis, Heart Lung 48 (1) (2019) 1–7.
[95] P. Di Pietro, R. Lizio, C. Izzo, V. Visco, A. Damato, E. Venturini, et al., A novel combination of high-load omega-3 lysine complex (AvailOm((R))) and anthocyanins exerts beneficial cardiovascular effects, Antioxidants 11 (5) (2022).
[96] L. Anchah, M.A. Hassali, M.S. Lim, M.I. Ibrahim, K.H. Sim, T.K. Ong, Health related quality of life assessment in acute coronary syndrome patients: the effectiveness of early phase I cardiac rehabilitation, Health Qual. Life Outcomes 15 (1) (2017) 10.
[97] R. Humphrey, M. Guazzi, J. Niebauer, Cardiac rehabilitation in Europe, Prog. Cardiovasc. Dis. 56 (5) (2014) 551–556.
[98] R. Belardinelli, I. Paolini, G. Cianci, R. Piva, D. Georgiou, A. Purcaro, Exercise training intervention after coronary angioplasty: the ETICA trial, J. Am. Coll. Cardiol. 37 (7) (2001) 1891–1900.
[99] P.A. Ades, M.H. Grunvald, R.M. Weiss, J.S. Hanson, Usefulness of myocardial ischemia as predictor of training effect in cardiac rehabilitation after acute myocardial infarction or coronary artery bypass grafting, Am. J. Cardiol. 63 (15) (1989) 1032–1036.
[100] M.A. Rogers, C. Yamamoto, J.M. Hagberg, J.O. Holloszy, A.A. Ehsani, The effect of 7 years of intense exercise training on patients with coronary artery disease, J. Am. Coll. Cardiol. 10 (2) (1987) 321–326.
[101] L. Anderson, N. Oldridge, D.R. Thompson, A.D. Zwisler, K. Rees, N. Martin, et al., Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis, J. Am. Coll. Cardiol. 67 (1) (2016) 1–12.
[102] U. Wisloff, A. Stoylen, J.P. Loennechen, M. Bruvold, O. Rognmo, P.M. Haram, et al., Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study, Circulation 115 (24) (2007) 3086–3094.
[103] K. Goel, R.J. Lennon, R.T. Tilbury, R.W. Squires, R.J. Thomas, Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community, Circulation 123 (21) (2011) 2344–2352.
[104] Q.R. Pack, K. Goel, B.D. Lahr, K.L. Greason, R.W. Squires, F. Lopez-Jimenez, et al., Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study, Circulation 128 (6) (2013) 590–597.
[105] C. Kim, D.Y. Kim, D.W. Lee, The impact of early regular cardiac rehabilitation program on myocardial function after acute myocardial infarction, Ann. Rehabil. Med. 35 (4) (2011) 535–540.
[106] D.G. Martinez, J.C. Nicolau, R.L. Lage, E. Toschi-Dias, L.D. de Matos, M.J. Alves, et al., Effects of long-term exercise training on autonomic control in myocardial infarction patients, Hypertension 58 (6) (2011) 1049–1056.
[107] A. Frank, M. Bonney, S. Bonney, L. Weitzel, M. Koeppen, T. Eckle, Myocardial ischemia reperfusion injury: from basic science to clinical bedside, Semin. Cardiothorac. Vasc. Anesth. 16 (3) (2012) 123–132.
[108] D.J. Hausenloy, D.M. Yellon, Myocardial ischemia-reperfusion injury: a neglected therapeutic target, J. Clin. Invest. 123 (1) (2013) 92–100.
[109] J. Shi, Y. Bei, X. Kong, X. Liu, Z. Lei, T. Xu, et al., miR-17-3p contributes to exercise-induced cardiac growth and protects against myocardial ischemia-reperfusion injury, Theranostics 7 (3) (2017) 664–676.
[110] H. Zhao, X. Chen, G. Hu, C. Li, L. Guo, L. Zhang, et al., Small extracellular vesicles from Brown adipose tissue mediate exercise Cardioprotection, Circ. Res. 130 (10) (2022) 1490–1506.
[111] J.L. Barber, K.N. Zellars, K.G. Barringhaus, C. Bouchard, F.G. Spinale, M. A. Sarzynski, The effects of regular exercise on circulating cardiovascular-related MicroRNAs, Sci. Rep. 9 (1) (2019) 7527.
[112] D. Wang, Y. Wang, J. Ma, W. Wang, B. Sun, T. Zheng, et al., MicroRNA-20a participates in the aerobic exercise-based prevention of coronary artery disease by targeting PTEN, Biomed. Pharmacother. 95 (2017) 756–763.
[113] Q. Yang, S. Chen, X. Wang, X. Yang, L. Chen, T. Huang, et al., Exercise mitigates endothelial Pyroptosis and atherosclerosis by downregulating NEAT1 through N6-Methyladenosine modifications, Arterioscler. Thromb. Vasc. Biol. 43 (6) (2023) 910–926.
[114] R. Gao, L. Wang, Y. Bei, X. Wu, J. Wang, Q. Zhou, et al., Long noncoding RNA cardiac physiological hypertrophy-associated regulator induces cardiac physiological hypertrophy and promotes functional recovery after myocardial ischemia-reperfusion injury, Circulation 144 (4) (2021) 303–317.
[115] W. Chen, Q. Ye, Y. Dong, Long term exercise-derived exosomal LncRNA CRNDE mitigates myocardial infarction injury through miR-489-3p/Nrf2 signaling axis, Nanomedicine 55 (2024) 102717.
[116] L. Wang, J. Feng, X. Feng, D. Meng, X. Zhao, J. Wang, et al., Exercise-induced circular RNA circUtrn is required for cardiac physiological hypertrophy and prevents myocardial ischaemia-reperfusion injury, Cardiovasc. Res. 119 (16) (2023) 2638–2652.
[117] M.A. Fischer, D.J. Chapski, E. Soehalim, D.J. Montoya, T. Grogan, M. Pellegrini, et al., Longitudinal profiling in patients undergoing cardiac surgery reveals postoperative changes in DNA methylation, Clin. Epigenetics 14 (1) (2022) 195.
[118] Z. Fang, U. Raza, J. Song, J. Lu, S. Yao, X. Liu, et al., Systemic Aging Fuels Heart Failure: Molecular Mechanisms and Therapeutic Avenues, ESC Heart Fail, 2024.
[119] H. Li, M.H. Hastings, J. Rhee, L.E. Trager, J.D. Roh, A. Rosenzweig, Targeting age-related pathways in heart failure, Circ. Res. 126 (4) (2020) 533–551.
[120] Y. Shi, H. Zhang, S. Huang, L. Yin, F. Wang, P. Luo, et al., Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials, Signal Transduct. Target. Ther. 7 (1) (2022) 200.
[121] N. Fujimoto, A. Prasad, J.L. Hastings, A. Arbab-Zadeh, P.S. Bhella, S. Shibata, et al., Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age, Circulation 122 (18) (2010) 1797–1805.
[122] C. Werner, M. Hanhoun, T. Widmann, A. Kazakov, A. Semenov, J. Poss, et al., Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis, J. Am. Coll. Cardiol. 52 (6) (2008) 470–482.
[123] B.C. Bernardo, J.Y.Y. Ooi, K.L. Weeks, N.L. Patterson, J.R. McMullen, Understanding key mechanisms of exercise-induced cardiac protection to mitigate disease: current knowledge and emerging concepts, Physiol. Rev. 98 (1) (2018) 419–475.
[124] A. Linke, V. Adams, P.C. Schulze, S. Erbs, S. Gielen, E. Fiehn, et al., Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle, Circulation 111 (14) (2005) 1763–1770.
[125] J.C. Campos, B.B. Queliconi, L.H.M. Bozi, L.R.G. Bechara, P.M.M. Dourado, A. M. Andres, et al., Exercise reestablishes autophagic flux and mitochondrial quality control in heart failure, Autophagy 13 (8) (2017) 1304–1317.
[126] V.D. Nair, Y. Ge, S. Li, H. Pincas, N. Jain, N. Seenarine, et al., Sedentary and trained older men have distinct circulating Exosomal microRNA profiles at baseline and in response to acute exercise, Front. Physiol. 11 (2020) 605.
[127] F. Giallauria, R. Lucci, A. De Lorenzo, M. D'Agostino, D. Del Forno, C. Vigorito, Favourable effects of exercise training on N-terminal pro-brain natriuretic peptide plasma levels in elderly patients after acute myocardial infarction, Age Ageing 35 (6) (2006) 601–607.

[128] N.A. Smart, T. Meyer, J.A. Butterfield, S.C. Faddy, C. Passino, G. Malfatto, et al., Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure, Eur. J. Prev. Cardiol. 19 (3) (2012) 428–435.
[129] F. Giallauria, P. Cirillo, M. D'Agostino, G. Petrillo, A. Vitelli, M. Pacileo, et al., Effects of exercise training on high-mobility group box-1 levels after acute myocardial infarction, J. Card. Fail. 17 (2) (2011) 108–114.
[130] C. Testa, A. Dil, A. Parlato, G. D'Ambrosio, A. Merolla, M. Pacileo, et al., Exercise for slowing the progression of atherosclerotic process: effects on inflammatory markers, Panminerva Med. 63 (2) (2021) 122–132.
[131] G. Billebeau, N. Vodovar, M. Sadoune, J.M. Launay, F. Beauvais, A. Cohen-Solal, Effects of a cardiac rehabilitation programme on plasma cardiac biomarkers in patients with chronic heart failure, Eur. J. Prev. Cardiol. 24 (11) (2017) 1127–1135.
[132] V. Visco, A. Robustelli, F. Loria, A. Rispoli, F. Palmieri, A. Bramanti, et al., An explainable model for predicting worsening heart failure based on genetic programming, Comput. Biol. Med. 182 (2024) 109110.
[133] C. Izzo, V. Visco, J. Gambardella, G.J. Ferruzzi, A. Rispoli, M.R. Rusciano, et al., Cardiovascular implications of microRNAs in coronavirus disease 2019, J. Pharmacol. Exp. Ther. 384 (1) (2023) 102–108.
[134] V. Visco, C. Esposito, A. Rispoli, P. Di Pietro, C. Izzo, F. Loria, et al., The favourable alliance between CardioMEMS and levosimendan in patients with advanced heart failure, ESC Heart Fail 11 (5) (2024) 2835–2848.
[135] P. Di Pietro, C. Izzo, A.C. Abate, P. Iesu, M.R. Rusciano, E. Venturini, et al., The dark side of sphingolipids: searching for potential cardiovascular biomarkers, Biomolecules 13 (1) (2023).
[136] D. Sorriento, M.R. Rusciano, V. Visco, A. Fiordelisi, F.A. Cerasuolo, P. Poggio, et al., The metabolic role of GRK2 in insulin resistance and associated conditions, Cells 10 (1) (2021).
[137] J.B.N. Moreira, M. Wohlwend, U. Wisloff, Exercise and cardiac health: physiological and molecular insights, Nat. Metab. 2 (9) (2020) 829–839.
[138] J. Taubel, W. Hauke, S. Rump, J. Viereck, S. Batkai, J. Poetzsch, et al., Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human phase 1b randomized, double-blind, placebo-controlled study, Eur. Heart J. 42 (2) (2021) 178–188.
[139] A. Ucar, S.K. Gupta, J. Fiedler, E. Erikci, M. Kardasinski, S. Batkai, et al., The miRNA-212/132 family regulates both cardiac hypertrophy and cardiomyocyte autophagy, Nat. Commun. 3 (2012) 1078.
[140] W.F. Penny, H.K. Hammond, Randomized clinical trials of gene transfer for heart failure with reduced ejection fraction, Hum. Gene Ther. 28 (5) (2017) 378–384.
[141] V. Cammisotto, C. Nocella, S. Bartimoccia, V. Sanguigni, D. Francomano, S. Sciarretta, et al., The role of antioxidants supplementation in clinical practice: focus on cardiovascular risk factors, Antioxidants 10 (2) (2021).
[142] M. Lagouge, C. Argmann, Z. Gerhart-Hines, H. Meziane, C. Lerin, F. Daussin, et al., Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha, Cell 127 (6) (2006) 1109–1122.
[143] D.M. Resurreccion, P. Moreno-Peral, M. Gomez-Herranz, M. Rubio-Valera, L. Pastor, J.M. Caldas de Almeida, et al., Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies, Eur. J. Cardiovasc. Nurs. 18 (1) (2019) 38–47.
[144] H.M. Dalal, P. Doherty, S.T. McDonagh, K. Paul, R.S. Taylor, Virtual and in-person cardiac rehabilitation, BMJ 373 (2021) n1270.
[145] J.C. Rawstorn, N. Gant, A. Direito, C. Beckmann, R. Maddison, Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis, Heart 102 (15) (2016) 1183–1192.
[146] M. Stefanakis, L. Batalik, V. Antoniou, G. Pepera, Safety of home-based cardiac rehabilitation: a systematic review, Heart Lung 55 (2022) 117–126.
[147] M. Scherrenberg, N. Marinus, F. Giallauria, M. Falter, H. Kemps, M. Wilhelm, et al., The need for long-term personalized management of frail CVD patients by rehabilitation and telemonitoring: a framework, Trends Cardiovasc. Med. 33 (5) (2023) 283–297.
[148] E. Thomas, R. Gallagher, S.L. Grace, Future-proofing cardiac rehabilitation: transitioning services to telehealth during COVID-19, Eur. J. Prev. Cardiol. 28 (7) (2021) e35–e36.
[149] K. Laudanski, D. Liu, J. Hajj, D. Ghani, W.Y. Szeto, Serum level of total histone 3, H3K4me3, and H3K27ac after non-emergent cardiac surgery suggests the persistence of smoldering inflammation at 3 months in an adult population, Clin. Epigenetics 14 (1) (2022) 112.