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*Review*

# Extracellular Vesicles in Myocardial Injury: Maladaptive Signaling and Exercise-Driven Cardiac Recovery

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**Abstract**

Cardiovascular diseases arise from diverse causes, including ischemia, inflammation, metabolic disorders, and cancer therapy-related injury; however, these diseases frequently converge on maladaptive myocardial remodeling and progression to heart failure. Extracellular vesicles (EVs), particularly exosomes, have emerged as key mediators of intercellular communication during myocardial injury and repair. In ischemic heart disease, endogenous exosomes exhibit clear temporal specificity, contributing to early stress responses and subsequently shaping post-ischemic healing by modulating inflammatory resolution, angiogenesis, metabolic recovery, and fibrotic remodeling. In addition to ischemia, EVs are also implicated in viral myocarditis and metabolic cardiomyopathies, where these particles influence immune responses and metabolic signaling and may serve as circulating biomarkers. Exercise represents an important physiological regulator of EV biology. Exercise-derived exosomes, as components of the broader exerkine network, transmit metabolic and anti-inflammatory signals that promote adaptive myocardial repair and help explain the biological effects of cardiac rehabilitation. This review summarizes current evidence on EV-mediated mechanisms underlying ischemic, inflammatory, metabolic, and therapy-related myocardial injury, with an emphasis on the associated potential clinical relevance as biomarkers and therapeutic targets.

**Keywords:** extracellular vesicles; exosomes; myocardial ischemia; recovery of function; exercise; cardiac rehabilitation; cardiomyopathies

## 1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality, largely due to the limited regenerative capacity of adult cardiomyocytes and the maladaptive remodeling that follows myocardial injury. While acute ischemic injury has traditionally dominated clinical and experimental paradigms, attention has increasingly shifted toward multi-etiological myocardial injury, encompassing metabolic cardiomyopathies such as diabetic cardiomyopathy (DCM), systemic inflammatory syndromes including sepsis-induced cardiomyopathy (SIC), and therapy-related cardiac dysfunction (TRCD) within the expanding field of cardio-oncology [1,2,3]. Despite distinct initiating insults, these conditions often converge on shared pathophysiological programs, including mitochondrial dysfunction, oxidative stress, immune dysregulation, and impaired intercellular communication, highlighting the need for integrative mechanisms of cardiac repair.

Over the past decade, exosomes—a subclass of small extracellular vesicles (30–150 nm) generated via the endosomal pathway—have been recognized as central mediators of cardiac cell–cell and organ–organ communication. By transporting biologically active cargos, including microRNAs, proteins, lipids, and metabolites, exosomes facilitate dynamic crosstalk among cardiomyocytes, fibroblasts, endothelial cells, and immune populations [4]. Exosomal signaling in the heart is highly context-dependent. Under pathological conditions such as DCM or SIC, disease-associated exosomes can propagate insulin resistance, mitochondrial stress, and excessive inflammatory responses, thereby exacerbating myocardial injury. In contrast, exosomes released from healthy, conditioned, or therapeutically primed cells exhibit cardioprotective properties, supporting anti-apoptotic signaling, metabolic homeostasis, and tissue repair [5,6,7,8,9,10]. This functional duality suggests that exosomes are not only biomarkers of cardiac injury but also active regulators of disease progression and recovery.

In metabolic and systemic inflammatory cardiomyopathies, exosomal dysregulation represents a key mechanistic component. In DCM, altered exosomal microRNA profiles have been linked to impaired glucose utilization, microvascular dysfunction, and progressive interstitial fibrosis [8,11]. In SIC, exosomes contribute to cytokine-driven myocardial depression, while also providing a potential platform for modulating excessive innate immune activation [12]. A similar duality is observed in cardio-oncology, where cancer therapy–induced cardiotoxicity—particularly from anthracyclines—is both associated with and potentially modifiable by distinct exosomal signatures reflecting mitochondrial injury, oxidative stress, and cardiomyocyte vulnerability [13].

Beyond pathological signaling, exercise acts as an important physiological modulator of exosome biology. Phys-

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ical activity induces the systemic release of exerkines, a class of exercise-responsive factors that are increasingly recognized to be packaged within circulating exosomes [14]. These exercise-derived exosomes (Ex-Exos) function as endocrine-like messengers that influence the myocardial microenvironment by enhancing mitochondrial fitness, supporting physiological hypertrophy, and increasing resilience to ischemic, metabolic, and inflammatory stressors [15,16]. Accordingly, exercise represents both a cornerstone of cardiac rehabilitation and a biologically grounded strategy for reshaping exosome-mediated signaling toward cardiac protection.

In this review, we examine the dual roles of extracellular vesicles (EVs) in myocardial injury and repair across ischemic, inflammatory, metabolic, and cancer therapy–related cardiac conditions, with particular emphasis on exercise-associated cardioprotection and cardiac rehabilitation. We further highlight key knowledge gaps concerning EV heterogeneity, cellular origin, cargo-specific functions, and clinical translation. By integrating pathological and exercise-responsive EV signaling, this review aims to identify shared mechanisms of myocardial injury and recovery and explore their implications for precision cardiovascular medicine.

## 2. Literature Review

### *2.1 Extracellular Vesicles in Ischemic and Ischemia–Reperfusion (I/R) Myocardial Injury*

Myocardial ischemia and ischemia–reperfusion (I/R) injury remain central drivers of cardiomyocyte loss and adverse remodeling. In addition to well-established mechanisms such as oxidative stress and mitochondrial dysfunction, extracellular vesicles (EVs) have been implicated as intermediates of intercellular communication within the injured myocardium. Rather than acting as passive byproducts, EVs appear to participate in both early stress responses and later phases of tissue remodeling, although the relative contribution of these phases varies substantially across experimental models [17,18,19].

#### 2.1.1 Exosomes as Endogenous Mediators of Cardioprotection During I/R

Ischemic stress activates not only cell-intrinsic survival pathways but also an intercellular cardioprotective network in which exosomes function as endogenous carriers of transferable protective signals. Early translational studies demonstrated that circulating plasma exosomes isolated from conditioned subjects attenuate myocardial I/R injury, supporting the concept that exosomes act as active mediators rather than passive biomarkers of cardioprotection [20]. Subsequent mechanistic studies showed that ischemic and remote ischemic preconditioning (IPC/RIPC) increase exosome release and that these vesicles convey cardioprotective signals across spatially distant organs. In a seminal study, RIPC-induced plasma exosomes reduced cardiomyocyte apoptosis and infarct size through transfer of exosomal *miR-24*, providing causal evidence for exosome-mediated ischemic tolerance [21].

Further work refined this paradigm by demonstrating temporal and molecular specificity within conditioning-associated exosome programs. Late-phase RIPC generates a distinct population of cardioprotective exosomes enriched in *miR-126a-3p*, which activates reperfusion injury salvage kinase (RISK) signaling and suppresses caspase-3–dependent apoptosis *in vivo* [22]. Endothelial cells have also been identified as a physiologically relevant source of cardioprotective exosomes, conferring resistance to simulated I/R injury in cardiomyocytes through extracellular signal-regulated kinases 1 and 2 (ERK1/2) mitogen-activated protein kinase (MAPK) signaling [23]. Together, these studies support a model in which ischemic conditioning programs endogenous exosome populations to transmit cardioprotective signals both locally and systemically.

Beyond acute cytoprotection, endogenous cardioprotective exosomes influence early post-ischemic remodeling. These vesicles modulate mitochondrial apoptosis, inflammatory amplification, and vascular responses through defined molecular cargos. Conditioning-associated exosomes enriched in heat-shock proteins, including HSP70 and HSP90, attenuate myocardial I/R injury by limiting complement activation and inflammatory signaling, thereby linking innate immune regulation to exosome-mediated cardioprotection [24,25]. Notably, endogenous exosome competence is preserved even under pathological conditions. In post–myocardial infarction heart failure models, plasma exosomes generated by ischemic preconditioning restored impaired cardioprotective responses, indicating that endogenous exosome programs can be reengaged when classical conditioning mechanisms are attenuated [26].

Endogenous cardioprotective exosomes also appear to link acute injury responses to subsequent reparative processes, although the strength of this linkage varies across experimental systems. For example, Chen et al. [24] demonstrated that plasma exosomes derived from remote ischemic conditioning improve post-infarction cardiac function and angiogenesis, in part through HSP70-associated mechanisms. In a more recent study, Yang et al. [27] identified a distinct role for ischemic preconditioning-induced serum exosomes, showing that *miR-133a-3p* transfer regulates replacement fibrosis by targeting *LTBP1* and *PPP2CA* during post-MI repair.

Evidence from cardiac-resident cell populations further supports a reparative role for EVs, but also points to mechanistic diversity. Early work by Chen et al. [28] demonstrated that cardiac progenitor cell–derived exosomes protect cardiomyocytes against acute I/R injury, Hao et al. [29] extended this concept by showing that exosomes from cardiac colony–forming cells enhance anti-apoptotic signaling via a *miR-221*–phosphatase and tensin homolog

(PTEN)/ phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) axis. More recently, Roefs et al. [30] reported that cardiac progenitor cell–derived EVs promote angiogenesis through both vesicle-associated and co-isolated protein cargos, suggesting a broader functional repertoire beyond microRNA transfer alone. Recent reviews converge on the view that endogenous EV programs integrate anti-apoptotic, anti-inflammatory, and pro-angiogenic signaling during myocardial ischemia and I/R injury [31,32]. At the same time, they emphasize translational challenges, including variability in EV composition and the limited extent of clinical validation [33].

While these studies establish exosomes as mediators of cardioprotection during ischemic stress, accumulating data indicate that exosome-mediated signaling extends beyond acute injury limitation to shape post-ischemic repair, immune resolution, and myocardial remodeling, as discussed below.

#### 2.1.2 Endogenous Exosomes as Regulators of Post-Ischemic Repair and Remodeling

Following myocardial infarction, long-term cardiac outcome is determined less by acute cardiomyocyte survival than by the efficiency of post-ischemic repair, including immune resolution, neovascularization, and scar maturation. Endogenous exosomes function as regulators during this reparative phase through mechanisms that are temporally and biologically distinct from acute cardioprotection. Rather than limiting infarct size, these vesicle-mediated programs influence cellular composition and signaling within the infarct border zone, thereby shaping ventricular remodeling and functional recovery.

2.1.2.1 Immune Resolution. Effective transition from inflammation to repair is essential for adaptive myocardial healing. Cardiac and circulating exosomes promote reparative macrophage phenotypes and suppress sustained pro-inflammatory signaling during the subacute post-MI phase. Exosomes derived from cardiac progenitor cells and mesenchymal stromal cells modulate macrophage polarization through defined microRNA cargos and associated proteins, facilitating clearance of necrotic tissue and inflammatory resolution [34]. EV-mediated immune modulation also influences chronic ventricular remodeling and progression to heart failure, highlighting exosomes as active regulators of post-ischemic immune homeostasis [35].

2.1.2.2 Angiogenesis and Metabolic Recovery in the Infarct Border Zone. Restoration of microvascular integrity and metabolic support in the peri-infarct region is critical for sustained repair. Endogenous exosomes released during the post-ischemic period enhance endothelial migration, proliferation, and tube formation through delivery of hypoxia-responsive microRNAs such as *miR-21* and *miR-210*, thereby increasing capillary density and regional perfusion during infarct healing [24,36].

Beyond microRNAs, EV-associated protein cargos also contribute to angiogenic repair. Cardiac progenitor cell–derived exosomes promote vascular regeneration through vesicle-bound proteins and co-isolated factors, supporting metabolic recovery of the injured myocardium [30].

2.1.2.3 Fibrosis Control and Scar Maturation. Endogenous exosomes also influence fibrotic remodeling and scar maturation, which determine ventricular compliance and long-term systolic function. Serum and cardiac exosomes generated after myocardial infarction regulate fibroblast activation and extracellular matrix deposition through delivery of anti-fibrotic microRNAs. Ischemic injury–induced serum exosomal *miR-133a-3p* limits replacement fibrosis and preserves ventricular architecture during chronic remodeling without affecting acute infarct size [27]. Mechanistic studies suggest that cardiac EVs modulate the balance between adaptive scar formation and pathological fibrosis, although mechanisms vary across models. Wang et al. [36] showed that cardiac progenitor cell–derived exosomal *miR-210* influences angiogenesis and cell survival, with potential indirect effects on extracellular matrix remodeling. In contrast, Feng et al. [37] highlighted EV-mediated crosstalk with fibroblasts, indicating a more direct role in regulating fibroblast activation during post-infarction remodeling. And more broadly, EVs have been described as a “double-edged sword”, capable of promoting repair or exacerbating fibrosis depending on their origin and cargo [38].

Collectively, these findings support a framework in which endogenous exosomes act as temporal regulators of myocardial repair, distinct from their role in acute ischemic cardioprotection. By coordinating immune resolution, angiogenesis, and scar maturation, exosome-mediated signaling influences whether post-ischemic remodeling proceeds toward adaptive healing or chronic dysfunction [31,33].

While endogenous exosomes contribute to post-ischemic repair, it is important to distinguish them from those induced by physiological stimuli such as exercise. Stress-induced cardioprotective EVs are typically released in response to ischemic injury or conditioning paradigms (e.g., ischemic preconditioning and remote ischemic conditioning), with effects closely linked to the acute phase of injury, including cytoprotection, early inflammatory modulation, and initiation of repair processes. Studies of remote ischemic conditioning further indicate that circulating exosomes are actively mobilized under ischemic stress and mediate organ protection through intercellular signaling pathways [39].

In contrast, exercise-derived EVs arise from coordinated systemic adaptation involving multiple tissues, including skeletal muscle, adipose tissue, and the vascular endothelium, rather than the injured myocardium alone. These vesicles are rapidly released into circulation during

exercise and function as mediators of inter-organ communication via cargos such as microRNAs and proteins. Functionally, exercise-responsive EVs are more closely associated with metabolic regulation, mitochondrial homeostasis, and immune modulation—processes that align with subacute and chronic phases of myocardial remodeling rather than immediate injury limitation.

This distinction is supported by recent studies positioning EVs within the broader "exerkine" network that governs systemic cardiometabolic adaptation [40], as well as cardiovascular-focused analyses emphasizing their role in sustaining mitochondrial and metabolic recovery [41]. Together, these findings indicate that endogenous and exercise-derived EVs represent complementary but temporally and functionally distinct signaling programs. Recognizing this difference provides a clearer framework for understanding how exercise influences post-ischemic cardiac repair, as discussed below.

#### 2.1.3 Exercise-Derived Exosomes as Reprogrammers of Post-Ischemic Repair

Exercise as a Physiological Reprogrammer of Post-Ischemic Repair Rather Than Acute Protection. Exercise training is a cornerstone of cardiac rehabilitation after myocardial infarction, yet its molecular mediators of post-ischemic repair remain incompletely defined. In contrast to endogenous cardioprotective EVs, which are primarily induced by ischemic stress and are closely associated with acute injury responses, exercise-derived EVs arise from systemic physiological adaptation and are not restricted to the injured myocardium. Rather than directly limiting acute ischemic injury, exercise appears to modulate the post-infarction environment through EV-mediated signaling. Exercise-derived exosomes (Ex-Exos), often discussed within the exerkine framework, have been proposed to act as endocrine-like messengers that coordinate immune and metabolic adaptation [40]. In parallel, recent review highlights their association with improved mitochondrial homeostasis, a key determinant of myocardial recovery [41].

Exercise-derived exosomes modulate immune resolution by shaping macrophage and immune cell function, dampening chronic low-grade inflammation, and promoting reparative immune phenotypes [42]. EVs released from exercise-conditioned cells carry regulatory microRNAs capable of suppressing inflammasome activation and pyroptotic signaling. Exercise-derived circulating exosomes enhance endothelial tube formation and vascular regeneration through microRNA transfer, independent of acute ischemic protection [43]. EV cargos induced by exercise further support mitochondrial biogenesis, mitophagy, and oxidative phosphorylation efficiency, processes essential for sustaining repaired myocardium [41].

In addition, exercise-reprogrammed EV signaling influences fibrotic remodeling. Exercise-associated EV cargos are biased toward anti-fibrotic and pro-adaptive remodeling programs, modulating fibroblast activation and extracellular matrix turnover [44]. Integrated analyses suggest that exercise shifts EV lipid and RNA profiles away from lipotoxic and pro-fibrotic signaling, aligning structural remodeling with functional recovery rather than pathological stiffening [45,46].

Together, these observations support a model in which exercise-derived exosomes act as physiological reprogrammers of post-ischemic repair. By coordinating immune resolution, angiogenesis, metabolic recovery, and fibrotic restraint, exercise-regulated EV programs bias myocardial remodeling toward long-term functional resilience [47].

### *2.2 Extracellular Vesicles in Viral Myocarditis: Mechanisms, Biomarkers, and Therapeutic Opportunities*

Viral myocarditis provides a distinct setting in which extracellular vesicles (EVs) can shape both cardiac injury and recovery. Unlike ischemic and ischemia–reperfusion injury—where EV signaling largely reflects sterile stress responses and endogenous cardioprotective programs—viral myocarditis involves ongoing viral replication, host immune activation, and EV-mediated intercellular communication. Available data suggest that EVs contribute to antiviral immune regulation and inflammatory amplification, and in some contexts may also facilitate viral dissemination and influence disease severity. For example, exosome-associated coxsackievirus B3 (CVB3) has been linked to enhanced viral spread and pathogenicity, and plasma exosomal microRNA patterns have been reported to track inflammatory activity in acute viral myocarditis [48,49].

#### 2.2.1 EV-Mediated Viral Propagation and Immune–Metabolic Reprogramming in Viral Myocarditis

EVs, particularly exosomes, can be exploited by cardiotropic viruses in ways that promote viral spread and reshape host responses in viral myocarditis. Fu and Xiong [48] showed that CVB3 can use host exosomes as transmission vehicles, expanding viral tropism to receptor-negative cells and aggravating myocardial injury. EV cargos may also affect downstream immune and metabolic programs. M2 macrophage–derived exosomes enriched in *lncRNA AK083884* attenuated CVB3-induced myocarditis by restraining PKM2/HIF-1α–dependent glycolytic reprogramming in macrophages [50]. Related work further suggests that virus-induced non-coding RNAs, including *miR-19a/19b*, can be selectively packaged into EVs and act as effectors of cardiomyocyte injury and immune activation [51].

Furthermore, recent reviews provide a more comprehensive mapping of these mechanisms. Xu et al. [52] integrate inflammation and myocardial repair into a unified therapeutic framework, whereas Zhu et al. [53] explore the potential of EV–virus crosstalk in diagnostics and delivery. Similarly, the role of disrupted protein quality control in driving disease progression has been highlighted by Mo-

hamud et al. [54]. Taken together, these insights support the view of EVs as active pathogenic drivers, with their specific contributions being highly contingent upon the viral environment and host-specific factors.

#### 2.2.2 Exosomal MicroRNAs as Diagnostic and Prognostic Biomarkers in Viral Myocarditis

In parallel with mechanistic studies, circulating exosomal microRNAs have been evaluated as non-invasive biomarkers for diagnosis and risk stratification in viral myocarditis. A clinical study identified a serum exosome-derived microRNA panel that discriminated fulminant myocarditis from other acute cardiac conditions, supporting the feasibility of EV-based liquid biopsy approaches [55]. Profiling studies have also reported remodeling of plasma exosomal microRNAs in acute viral myocarditis, with enrichment of immune- and inflammation-related pathways [49]. Similar observations have been described in pediatric fulminant myocarditis, where disease-associated exosomal microRNA patterns correlated with clinical severity [56]. Reviews highlight potential advantages of EV-associated microRNAs over free-circulating microRNAs, including increased stability and, in some settings, improved disease specificity [47,57]. Taken together, current data support exosomal microRNAs as a mechanistically informed biomarker class with translational relevance for viral myocarditis [58].

#### 2.2.3 Therapeutic Exploitation of Native and Engineered EVs in Viral Myocarditis

EVs have also been explored as therapeutic agents and delivery platforms in viral myocarditis. Engineered EVs with immunomodulatory properties were reported to suppress myocardial inflammation, reduce viral burden, and limit adverse remodeling in experimental models [59]. EV-based antigen delivery has likewise been investigated, including VP1-loaded exosomes that enhanced host resistance to CVB3 infection in preclinical studies [60]. Mesenchymal stem cell–derived exosomes (MSC-Exos) represent another widely studied approach; for example, hUCMSC-derived exosomes alleviated viral myocarditis via AMPK/mTOR-dependent autophagy activation [61] and reduced cardiomyocyte ferroptosis through exosomal *let-7a-5p* [62].

More recent studies further highlight the importance of EV source and composition. Platelet-derived EVs exhibit therapeutic effects that correlate with their biomolecular content [63], while cardiac progenitor cell–derived exosomes have been shown to attenuate CVB3-induced apoptosis through modulation of mTOR signaling [64]. In contrast, donor-dependent heterogeneity in adipose-derived EVs has been associated with variable therapeutic outcomes [65]. In addition, large EVs derived from preconditioned cardiomyocytes can modulate macrophage polarization and reduce myocardial inflammation via p38 MAPK signaling [66]. These findings suggest that EVs can function as both biologically active therapeutics and adaptable delivery platforms; however, their efficacy appears highly dependent on cellular origin, cargo composition, and experimental context.

#### 2.2.4 Translational Perspectives and Unresolved Challenges

Several barriers continue to impede the clinical transition of EV-based diagnostics and therapies. Beyond the foundational issues of isolation and scalability [67], the literature reveals a divergence in how these limitations are contextualized. On one hand, some analyses focus on specific pathways, such as the EV-autophagy axis in stress modulation [68]; on the other, broader frameworks integrate EVs into the complex landscape of viral pathogenesis [69]. The clinical outlook is further shaped by recent cardiovascular syntheses that place viral myocarditis within the context of inflammatory cardiomyopathies [70]. While there is significant enthusiasm for EVs as diagnostic and therapeutic agents, practical constraints in delivery systems remain a central theme [71], even as targeted strategies like MSC-derived EVs offer new hope for cardiac regeneration [72]. Ultimately, as emphasized in recent translational perspectives [52], bridging the gap between promise and practice will require a concerted effort toward standardization and a more rigorous, mechanism-based design.

### *2.3 Extracellular Vesicles as Metabolic Integrators in Myocardial Injury*

Metabolic myocardial injury arises from chronic systemic metabolic disorders, including diabetes, obesity, insulin resistance, and lipid overload. Unlike acute ischemic or inflammatory insults, metabolic myocardial injury develops gradually and is closely linked to mitochondrial dysfunction, oxidative stress, impaired substrate utilization, and maladaptive intercellular communication within the cardiac microenvironment. Growing data indicate that extracellular vesicles (EVs), particularly exosomes, participate in this pathological crosstalk by integrating systemic metabolic cues with local cardiac responses [8]. Acting as carriers of microRNAs, lipids, metabolites, and proteins, EVs link extracardiac metabolic stress to cardiomyocyte dysfunction, endothelial rarefaction, fibroblast activation, and chronic low-grade inflammation. This EV-mediated signaling network provides a mechanistic framework for understanding how metabolic stress is amplified and propagated within the heart, with particular relevance to diabetic and obesity-related cardiomyopathies. This section summarizes recent advances defining EV-driven metabolic reprogramming and mitochondrial injury in metabolic myocardial disease, as well as emerging implications for biomarker development and therapeutic intervention [7].

#### 2.3.1 Diabetic Cardiomyopathy: EV-Mediated Cardiomyocyte–Endothelial–Fibroblast Crosstalk

Diabetic cardiomyopathy (DCM) is increasingly viewed as a disorder of disrupted intercellular communication, in which small extracellular vesicles (sEVs) mediate pathogenic signaling among cardiomyocytes, endothelial cells, fibroblasts, and metabolically active adipose tissue. Rather than serving solely as markers of metabolic stress, sEVs actively transfer microRNAs and other cargo that influence angiogenesis, fibrotic remodeling, and mitochondrial homeostasis under diabetic conditions. Recent reviews consistently identify EV-mediated signaling as a key mechanistic layer linking hyperglycemia and insulin resistance to structural cardiac remodeling in DCM [8,73].

A foundational example of cardiomyocyte–endothelial EV communication was reported by Wang et al. [18] who showed that cardiomyocytes exposed to diabetic stress release exosomes enriched in *miR-320*. Uptake of these vesicles by endothelial cells suppressed angiogenic programs through inhibition of IGF-1 signaling, contributing to microvascular rarefaction in type 2 diabetes [18]. Although published earlier, this study remains central to current models of EV-mediated endothelial dysfunction in DCM.

More recent work has extended EV signaling to the cardiomyocyte–fibroblast axis. A 2024 study demonstrated that cardiomyocyte-derived sEVs normally exert anti-fibrotic effects via delivery of *miR-194-3p*, which suppresses TGFβR2 signaling in cardiac fibroblasts. Under diabetic conditions, reduced incorporation of *miR-194-3p* into cardiomyocyte sEVs removes this restraint, promoting fibroblast activation and extracellular matrix deposition [74]. These findings indicate that diabetes disrupts protective EV-mediated homeostatic signaling within the myocardium.

Beyond local interactions, extracardiac EV signaling—particularly from adipose tissue—further fuels myocardial injury in diabetes. For instance, dysfunctional adipocyte-derived sEVs enriched in *miR-130b-3p* have been shown to exacerbate diabetic ischemia–reperfusion injury by triggering a cascade of oxidative stress and mitochondrial-dependent apoptosis [75,76]. These findings underscore a systemic model of DCM, where the disruption of EV-mediated crosstalk between cardiomyocytes, endothelial cells, fibroblasts, and adipocytes converges on a triad of impaired angiogenesis, maladaptive fibrosis, and metabolic injury. Building on this network-wide perspective, Zhang et al. [77] and Chandrasekera and Katare [78] have further explored the therapeutic and regulatory potential of these vesicles. Collectively, these syntheses solidify the concept of "EV-mediated network disruption", while also acknowledging that EV cargo and function are highly contingent upon the specific disease environment.

#### 2.3.2 Obesity and Epicardial Adipose Tissue–Derived EVs: Adipose–Heart Communication

In obesity, myocardial injury often arises in the setting of chronic adipose dysfunction, where extracellular vesicles released from expanded fat depots convey lipotoxic and inflammatory signals to the heart. These signals promote cardiomyocyte metabolic inflexibility, microvascular dysfunction, fibroblast activation, and ventricular remodeling. Epicardial adipose tissue (EAT) is of particular interest because of its anatomical proximity and shared microcirculation with the myocardium, positioning EAT-derived EVs as short-range mediators of adipose–heart communication. This concept is supported by *in vivo* evidence demonstrating that epicardial fat EVs directly remodel cardiac tissue and worsen structural and electrical phenotypes [79].

Shaihov-Teper et al. [79] showed that EVs released from epicardial fat induce cellular and electrophysiological remodeling consistent with atrial fibrosis and myopathy. Importantly, injection of human epicardial fat EVs into rat myocardium reproduced these effects *in vivo*, supporting a causal role for epicardial fat EVs in cardiac remodeling rather than a purely associative biomarker signal [79]. Although focused on atrial remodeling, this work has direct implications for metabolic myocardial injury by demonstrating that EAT-derived EVs actively influence myocardial inflammatory and fibrotic pathways.

Obesity also alters EV output from visceral white adipose tissue (WAT). Su and colleagues [80] demonstrated that epididymal WAT promotes angiotensin II–induced cardiac fibrosis in an exosome-dependent manner through an exosomal *miR-23a-3p–RAP1* pathway in cardiac fibroblasts. Interventions targeting adipose tissue, exosome biogenesis, or *miR-23a-3p* each attenuated fibrosis and dysfunction, providing strong causal evidence for adipocyte-derived EVs as long-range profibrotic mediators [80]. Immune cell–derived EVs further contribute to obesity-related myocardial injury. Adipose tissue macrophage–derived exosomes from obese mice were shown to induce cardiomyocyte ferroptosis via delivery of *miR-140-5p*, which suppresses SLC7A11-dependent glutathione synthesis and promotes lipid peroxidation, mitochondrial injury, and systolic dysfunction [81]. In parallel, hypertrophic adipocytes can impair myocardial insulin signaling through EV-mediated microRNA transfer. Wen and colleagues [82] demonstrated that adipocyte-derived exosomal *miR-802-5p* induces insulin resistance in cardiomyocytes by downregulating HSP60. Together, these studies refine obesity-related cardiomyopathy as a mechanistically defined process driven by adipose immune–stromal EV signaling.

Not all adipose-derived EVs exert detrimental effects. Brown adipose tissue–derived exosomes (BAT-Exos) improved systemic metabolism in high-fat diet models and were associated with improved cardiac function [83]. Consistent with this, adipose tissue–derived EVs were shown to protect the heart against ischemia–reperfusion injury *in vivo*

[84]. These findings suggest that depot-specific adipose EV programs may be leveraged therapeutically, supporting EV cargo–guided strategies for metabolic myocardial injury.

#### 2.3.3 Exercise-, Immune–Metabolism–Regulated, and Therapeutic EVs

In contrast to maladaptive EV signaling in diabetes and obesity, exercise and immune–metabolic reprogramming can reshape the EV landscape toward cardioprotection. Exercise induces systemic release of bioactive factors, collectively termed exerkines, among which EVs have emerged as stable mediators of metabolic adaptation. EVs have been proposed as integral components of the exerkine network, coordinating glucose and lipid utilization, mitochondrial biogenesis, and inflammatory restraint across metabolic organs, with relevance to diabetic cardiomyopathy and obesity-related cardiac remodeling [40].

Exercise-modulated EVs are closely linked to mitochondrial quality control, a central determinant of metabolic myocardial injury. A synthesis in Journal of the American Heart Association highlighted that exercise improves mitochondrial homeostasis, including mitophagy, oxidative phosphorylation efficiency, and redox balance, in part through EV-mediated transfer of regulatory RNAs and proteins between skeletal muscle, immune cells, and the heart [41]. These observations support a role for exercise-derived EVs in counteracting mitochondrial dysfunction underlying metabolic cardiomyopathies.

Therapeutic EVs provide further mechanistic support for reversibility of metabolic myocardial injury. Mesenchymal stem cell–derived exosomes attenuated inflammation and cardiomyocyte pyroptosis in diabetic cardiomyopathy by delivering *miR-223-3p*, which suppressed NLRP3 inflammasome activation and improved cardiac structure and function [85]. Immune cell–derived EVs also illustrate immune–metabolic crosstalk. Reviews describe how alternatively activated macrophages release exosomes enriched in *miR-690*, which enhances insulin sensitivity and dampens inflammatory signaling, offering a conceptual framework that may extend to cardiac metabolic stress and remodeling [46,86].

These therapeutic and exercise-related studies are embedded within a rapidly expanding literature defining EV functions in cardiometabolic disease. Recent reviews synthesize EV roles as biomarkers, mediators, and therapeutic vectors across cardiomyopathies [44,47]. Conceptual models further describe EVs as metabolic bridges integrating lipid signaling, immune modulation, and mitochondrial adaptation in cardiac repair [45]. Together, these data support a framework in which exercise-induced, immune-regulated, and engineered EVs converge on shared metabolic–mitochondrial pathways to mitigate myocardial injury, positioning EVs as actionable targets for translational intervention in metabolic cardiomyopathy.

### *2.4 Extracellular Vesicles in Cardio-Oncology.*

#### 2.4.1 Clinical Imperative: Why Upstream Biomarkers Are Needed in Immune Checkpoint Inhibitor (ICI) Cardiotoxicity

ICI–associated myocarditis is uncommon but carries a high mortality risk, often presenting early after treatment initiation and progressing rapidly to malignant arrhythmias, heart failure, or cardiovascular death [87]. Current guidelines recommend baseline cardiovascular assessment and intensified monitoring during early treatment cycles, typically based on symptoms, electrocardiography, and serial high-sensitivity troponin measurements, because timely immunosuppression can improve outcomes when initiated early [1,88]. However, both troponin elevation and electrocardiographic abnormalities largely reflect downstream cardiomyocyte injury rather than the upstream immune activation that initiates myocarditis [89,90]. As a result, surveillance strategies face limitations in specificity and clinical decision thresholds, particularly in oncology patients who frequently have competing causes of biomarker elevation [91,92,93,94].

#### 2.4.2 Tumor–Heart Axis: EVs as Long-Range Modulators of Cardiac Vulnerability

Beyond direct therapy-related cardiotoxicity, growing evidence supports a bidirectional tumor–heart axis in which cardiovascular injury influences tumor behavior through long-range extracellular vesicle (EV) signaling. Myocardial infarction (MI), a common comorbidity in patients with cancer, has been shown to accelerate tumor progression by reprogramming innate immune responses and altering systemic inter-organ communication. In murine models, MI promoted the growth of E0771 and MMTV-PyMT breast tumors via epigenetic reprogramming of innate immunity, creating a systemic environment permissive for tumor expansion [95]. Small extracellular vesicles (sEVs) have emerged as critical mediators of this process.

sEVs function as nanoscale carriers of bioactive molecules that influence not only the tumor microenvironment—including cancer cells, stromal cells, and immune cells—but also distant organs. Caller and colleagues [96] demonstrated that exosomes isolated from cardiac tissue fragments harvested 10 days after MI increased Lewis lung carcinoma cell proliferation and migration in a dose-dependent manner. Consistent with their capacity for long-range trafficking, MI markedly increased the accumulation of cardiac sEVs in the lung, a preferential site of tumor metastasis [97].

MI-induced sEVs also reprogram immune components of the tumor microenvironment. Mesenchymal stem cell–derived sEVs released after MI enhanced macrophage proangiogenic and protumorigenic phenotypes, increasing inducible nitric oxide synthase (iNOS) and programmed death ligand 1 (PD-L1) expression and promoting secretion of inflammatory and angiogenic mediators [96]. Although

conditioned media from sEV-exposed macrophages did not directly stimulate tumor cell proliferation, it robustly enhanced endothelial migration and tube formation, implicating angiogenesis as a key downstream effector of MI-driven EV signaling.

Pharmacological inhibition studies further support a central role for sEVs in tumor–heart crosstalk. Treatment with GW4869, an inhibitor of ceramide-dependent sEV biogenesis, suppressed tumor growth following MI and produced similar antitumor effects in sham-operated animals, suggesting concurrent depletion of pro-tumorigenic EVs derived from extracardiac sources such as bone marrow, spleen, and tumor tissue [96,98]. Independent work has shown that tumor-derived sEVs educate immune cells in distant organs and promote pre-metastatic niche formation [98,99].

Reciprocal effects of tumor-derived EVs on the heart have also been described. Exosomes released after MI enhanced the survival of lung cancer and osteosarcoma cells by desensitizing them to ferroptosis [100]. In parallel, circulating tumor-derived EVs aggravated myocardial ischemia–reperfusion injury *in vivo* by delivering *miR-485-3p* to cardiomyocytes and suppressing PGC-1α–dependent mitochondrial bioenergetics; inhibition of EV release mitigated cardiac injury and fibrosis [101]. Tumor EVs have also been implicated in cancer cachexia, where EV-associated microRNAs drive skeletal muscle wasting; given shared remodeling pathways between skeletal and cardiac muscle, these signals provide a plausible mechanism for subclinical cardiac remodeling in cachectic states [102,103]. Together, these findings identify EVs as bidirectional mediators of tumor–heart communication, linking myocardial injury, tumor progression, and susceptibility to subsequent cardiotoxic therapies.

#### 2.4.3 Exosomes/EVs in Anthracycline (DOX) Cardiotoxicity

Anthracyclines, particularly doxorubicin (DOX), remain widely used in oncology but are limited by cumulative dose–dependent cardiotoxicity and long-term heart failure risk. DOX induces oxidative stress, mitochondrial dysfunction, and regulated cardiomyocyte death pathways. EV biology intersects with these processes at two levels: cardiomyocyte-derived EVs as early indicators of injury and tumor-derived EVs as amplifiers of cardiac damage during chemotherapy.

In murine models of DOX cardiotoxicity, circulating EVs increased early and carried proteomic signatures of myocardial stress and oxidized proteins, supporting their potential as minimally invasive indicators that precede conventional biomarkers of overt injury [104]. Complementary translational studies suggest that EV cargo stability and tissue specificity may offer advantages over soluble biomarkers for monitoring DOX-induced cardiac injury [105].

Recent work further implicates tumor-derived EVs in amplifying anthracycline cardiotoxicity. A Redox Biology study showed that sEVs released from DOX-treated breast cancer cells exacerbated ferroptosis in human iPSC-derived cardiomyocytes, identifying EV microRNA cargo as a mechanistic driver of injury amplification [106]. Similarly, breast cancer–derived exosomal *miR-216a-5p* was shown to promote cardiomyocyte pyroptosis via an itchy E3 ubiquitin protein ligase/thioredoxin-interacting protein/NLR family pyrin domain containing 3 (ITCH/TXNIP/NLRP3) signaling axis, and inhibition of EV release or miRNA targeting attenuated cardiac injury [107]. These findings support a model in which chemotherapy reshapes tumor EV output, which in turn feeds back to the heart to intensify regulated cell death pathways. EV engineering strategies aimed at mitigating DOX cardiotoxicity or improving drug delivery are under investigation, although preserving antitumor efficacy remains a key translational challenge [108,109].

#### 2.4.4 EVs in ICI-Associated Myocarditis

EVs are also emerging as mechanistic mediators and candidate early biomarkers in ICI-associated myocarditis. Although direct clinical evidence is limited, experimental studies support EV-mediated immune–cardiac communication preceding overt myocardial injury. PD-1 blockade reprograms macrophage-derived exosomal cargo, enriching *miR-34a-5p*, which is transferred to cardiomyocytes and induces senescence and dysfunction by suppressing PNUTS-dependent protective signaling [110]. Complementary studies have identified gasdermin E–mediated pyroptosis and mitochondrial cGAS–STING activation as central drivers of ICI myocarditis [111], suggesting that EVs carrying mitochondrial or inflammatory signals may appear in circulation earlier than necrosis-associated biomarkers such as troponin.

From a clinical perspective, early detection is critical because prompt initiation of high-dose corticosteroids improves outcomes in ICI myocarditis [91]. EVs offer theoretical advantages as upstream biomarkers, including molecular stability, integration of immune and metabolic signals, and accessibility through minimally invasive sampling. However, EV-based biomarkers in this setting remain exploratory, and prospective human studies demonstrating incremental value over established surveillance strategies are still lacking [87,88].

Together, these mechanistic and translational observations have prompted increasing interest in extracellular vesicles as candidate upstream biomarkers for the early detection and risk stratification of immune checkpoint inhibitor–associated cardiotoxicity (Table 1, Ref. [87,88,101,104,106,107,108,110,111,112]). The proposed candidates span EV burden, cellular origin, and mechanistically informed cargo, including immune cell–derived EVs enriched in *miR-34a-5p* in immune-mediated myocarditis,

**Table 1. Extracellular vesicle–based candidate biomarkers across immune checkpoint inhibitor– and anthracycline-associated cardiotoxicity**.

| EV candidate | Therapy context | EV source | Sample & timing | Assay/platform | Intended clinical use | Evidence level | Key mechanistic/translational findings | Key references |
|---|---|---|---|---|---|---|---|---|
| EV-associated *miR-34a-5p* | ICI | Immune cells (macrophages) | Plasma; baseline and early cycles (C1–C2) | EV isolation + ddPCR/small RNA-seq | Early prediction; mechanism-informed risk stratification | Mechanistic (cell/animal); translational | PD-1 blockade reprograms macrophage EV cargo, transferring *miR-34a-5p* to cardiomyocytes and inducing senescence/dysfunction via PNUTS suppression | Xia et al., J Immunother Cancer 2020 [110] |
| Total circulating EV burden/size distribution | ICI + Anthracycline | Mixed (immune, tumor, cardiac) | Plasma; serial early monitoring | NTA; high-sensitivity flow cytometry | Screening; risk enrichment | Exploratory; indirect clinical | Systemic immune activation or chemotherapy stress increases EV release, potentially preceding overt myocardial injury | Kumar et al., STTT 2024 [112] |
| Immune cell–derived EV subsets ($CD45^+$, $CD14^+$ EVs) | ICI | Leukocytes/ macrophages | Plasma; early treatment | High-sensitivity flow cytometry; ExoView (NanoView Biosciences, Boston, MA, USA) | Mechanistic stratification | Exploratory | Reflect immune activation states implicated in immune-related myocarditis | Moslehi et al., JCI 2021 [88] |
| Cardiomyocyte-derived EV proteomic signatures | Anthracycline (DOX) | Cardiomyocytes | Plasma; early after DOX exposure | EV proteomics (LC–MS/MS) | Early detection of subclinical injury | Animal + translational | Cardiomyocyte-released EVs contain early injury-associated proteins before overt dysfunction | Yarana et al., Clin Cancer Res 2018 [104] |
| Tumor-derived EV *miR-485-3p* | Anthracycline/tumor–heart axis | Tumor cells | Plasma; pre-treatment or early therapy | EV miRNA profiling | Baseline vulnerability assessment | Animal | Tumor EVs exacerbate cardiac stress by suppressing PGC-1α–dependent mitochondrial bioenergetics | Mei et al., Adv Sci 2025 [101] |

**Table 1. Continued.**

| EV candidate | Therapy context | EV source | Sample & timing | Assay/platform | Intended clinical use | Evidence level | Key mechanistic/translational findings | Key references |
|---|---|---|---|---|---|---|---|---|
| Tumor-derived sEV miRNAs promoting ferroptosis | Anthracycline (DOX) | Breast cancer cells | Conditioned media; plasma (translational) | EV isolation + functional assays | Mechanistic amplification of injury | Mechanistic (human iPSC-CMs) | DOX-treated tumor cells secrete sEVs that worsen cardiomyocyte ferroptosis | Han et al., Redox Biology 2025 [106] |
| Exosomal *miR-216a-5p* | Anthracycline (DOX) | Breast cancer cells | Plasma/ conditioned media | EV miRNA analysis | Early prediction; therapeutic targeting | Mechanistic + translational | Tumor–heart EV transfer triggers cardiomyocyte pyroptosis via ITCH/TXNIP/NLRP3 axis | Ma et al., STTT 2025 [107] |
| MSC-derived protective EV miRNAs (e.g., *miR-96*) | Anthracycline (DOX) | MSCs | Plasma/ therapeutic EVs | EV isolation + miRNA assays | Cardioprotection | Preclinical | MSC EVs attenuate DOX cardiotoxicity via anti-apoptotic and mitochondrial pathways | Lei et al., JAHA 2021 [108] |
| EV cargo reflecting pyroptosis/mitochondrial stress | ICI | Cardiomyocytes/ immune cells | Plasma; early myocarditis suspicion | Targeted EV proteomics/ miRNA panels | Early detection; severity stratification | Mechanistic | Pyroptosis- and cGAS–STING–linked pathways precede necrosis-derived biomarkers | Sun et al., Nat Commun 2024 [111] |
| Composite EV signature (burden + phenotype + cargo) | ICI + Anthracycline | Mixed | Longitudinal plasma sampling | Multimodal EV profiling | Integrated risk prediction model | Conceptual/ emerging | EV metrics may provide incremental value over troponin and ECG in early risk models | Herrmann et al., JAMA Oncol 2026 [87] |

Table 1: Extracellular vesicle (EV) candidates are proposed as exploratory biomarkers for early detection and risk stratification of immune checkpoint inhibitor– and anthracycline-associated cardiotoxicity. Evidence ranges from mechanistic to translational studies; none are clinically validated. EV readouts are intended to complement, not replace, guideline-recommended surveillance. ICI, immune checkpoint inhibitor; LC–MS/MS, liquid chromatography–tandem mass spectrometry; ECG, electrocardiogram; ITCH, itchy E3 ubiquitin protein ligase; TXNIP, thioredoxin-interacting protein; NLRP3, NLR family pyrin domain containing 3.

as well as tumor- or cardiomyocyte-derived EV signatures relevant to therapy-related injury.

Longitudinal EV profiling during early treatment cycles therefore represents a promising strategy to refine risk stratification in cardio-oncology. Future studies should prioritize validation of EV burden, cellular origin, and biologically grounded cargo within well-characterized clinical cohorts. In parallel, standardization of pre-analytical workflows and demonstration of predictive value beyond existing tools will be essential to support clinical translation of EV-based surveillance approaches.

### *2.5 Exercise-Responsive Exosomes as Mediators of Cardiac Rehabilitation*

Exercise-based cardiac rehabilitation is a cornerstone of secondary prevention after myocardial injury, yet the molecular pathways linking physical activity to sustained cardioprotection remain incompletely defined [113,114]. Recent work points to extracellular vesicles (EVs) as systemic mediators of exercise-induced repair and functional recovery, adding a vesicle-based layer of inter-organ communication to traditional hemodynamic explanations [10]. Exercise triggers coordinated EV release from skeletal muscle, adipose tissue, vascular endothelium, and the heart, reshaping the circulating vesicle pool [115,116].

Functionally, these exercise-responsive EVs carry bioactive cargos that influence several aspects of myocardial recovery. For example, exercise-derived exosomal *miR-342-5p* has been shown to mediate cardioprotective effects after ischemic injury [43], while adipose-derived EVs carrying *miR-17-3p* have been linked to reduced programmed necrosis in ischemia–reperfusion models [84]. The impact of exercise-induced EV signaling is far more expansive, modulating everything from angiogenesis to immune resolution [10]. Of particular interest is the ability of these EVs to shift macrophage polarization toward a pro-healing state, although we must bridge the gap between current *in vitro* findings and human clinical reality [117,118].

Ultimately, these observations position EVs as central players in the "pleiotropic benefits" of physical activity. By acting as both mediators and biomarkers, EVs provide a robust framework for the emerging field of "rehabilomics", offering a path toward precision cardiac rehabilitation and a deeper understanding of why patients respond differently to exercise interventions [16,119].

#### 2.5.1 Sources and Cargo of Exercise-Induced EVs

Exercise induces a rapid, stimulus-dependent rise in circulating EVs, consistent with EV release as an early, regulated component of systemic adaptation rather than a non-specific injury byproduct [117]. Acute bouts and chronic training alter EV abundance, subtype distribution, and surface-marker profiles, suggesting that cellular sources vary with modality and intensity [120,121]. In human studies, platelets, endothelial cells, and leukocytes account for a substantial fraction of the exercise-responsive EV pool, highlighting vascular and hematologic compartments as major contributors early during exercise [120]. Exercise physiology frameworks place EVs within the broader set of "exerkines", emphasizing vesicular packaging as a mechanism that can stabilize bioactive signals and potentially bias delivery to recipient tissues [122].

Skeletal muscle is considered a major contributor to exercise-induced circulating EVs, based on studies demonstrating increased EV release and enrichment of vesicle-associated proteins and candidate myokines within circulating EV fractions following exercise [115]. However, direct attribution of EV origin remains technically challenging, and current evidence is largely based on indirect profiling approaches. Endothelial-derived EVs respond to hemodynamic shear stress and may support vascular repair programs relevant to cardiac rehabilitation; exercise-associated EV preparations have been reported to enhance endothelial repair capacity in experimental settings [123]. Adipose tissue–derived EVs also contribute to the exercise-responsive landscape, and adipose exosomal microRNAs (e.g., *miR-17-3p*) have been linked to protection against myocardial ischemia–reperfusion injury, supporting a plausible adipose–heart EV axis during rehabilitation [84].

At the cargo level, exercise modifies EV microRNAs, proteins, and other biomolecules in a dose- and context-dependent manner [116,121]. Resistance exercise can alter EV size distributions and subpopulation characteristics, with sex-specific patterns reported in healthy cohorts [124]. Hypoxic versus normoxic exercise has also been associated with differences in exosome-like vesicle concentrations and markers of multivesicular body biogenesis, suggesting that oxygen tension and metabolic stress influence EV biogenesis and cargo loading [125]. Methodological reviews note that pre-analytical variables and co-isolated contaminants (e.g., lipoproteins) can confound cargo attribution, reinforcing the need for standardized workflows and reporting [118,126]. Overall, current data support a multi-source model in which exercise-responsive EVs carry coordinated cargo signatures with potential relevance to metabolism, redox balance, angiogenesis, and immune tone during rehabilitation [116,121].

#### 2.5.2 Functional Effects of Exercise-Induced EVs on the Injured Heart

In ischemic cardiomyopathy, including myocardial infarction and ischemia–reperfusion (I/R) injury, exercise-induced EVs have the strongest supporting evidence as functional mediators linking physical activity to myocardial repair. Experimental studies show that acute and chronic exercise increase circulating small EVs, and transfer of these EVs to sedentary or injured recipients can reduce infarct size and improve post-ischemic recovery [117,123]. Mechanistically, exercise-responsive EVs are enriched in cardioprotective microRNAs and proteins reported to sup-

press apoptosis, limit oxidative and mitochondrial stress, and support endothelial repair and angiogenesis. In a landmark study, long-term exercise increased circulating exosomal *miR-342-5p*, which inhibited cardiomyocyte apoptosis and improved cardiac function after I/R injury, providing causal evidence that EV cargo can transmit exercise-associated cardioprotection [43].

Exercise-induced EVs may also influence inflammatory resolution by shifting macrophage phenotypes toward reparative states and supporting microvascular integrity, processes central to favorable ventricular remodeling during rehabilitation [10]. Reviews integrating animal and human data further note that EV-mediated protection varies with exercise dose, intensity, and timing relative to ischemic insult, reinforcing the relevance of structured rehabilitation rather than unstandardized physical activity [16]. Together, these findings support ischemic cardiomyopathy as the context in which exercise-induced EVs most convincingly function as active effectors of repair rather than passive correlates of adaptation.

#### 2.5.3 Effects of Exercise-Induced EVs on Diabetic Cardiomyopathy

In diabetic cardiomyopathy (DCM), the role of exercise-induced EVs is less direct but increasingly plausible. Diabetes alters EV biogenesis and cargo composition in ways that favor pro-inflammatory, pro-fibrotic, and metabolically maladaptive signaling, contributing to myocardial stiffness, microvascular dysfunction, and energetic inefficiency [127]. Exercise training can partially reshape this circulating EV landscape, including restoration of endothelial- and adipose-derived EV functions relevant to vascular repair and metabolic homeostasis [116,128]. In type 2 diabetes cohorts, exercise has been associated with improved angiogenic capacity of circulating EVs and enhanced EV-mediated endothelial migration and nitric oxide signaling, suggesting a route by which exercise-responsive EVs could reduce vascular dysfunction linked to DCM [129].

Direct causal evidence that exercise-induced EVs reverse established diabetic remodeling remains limited. Many mechanistic studies focus on pathological EVs from diabetic cardiomyocytes or immune cells, rather than EVs generated in response to exercise interventions [127,129]. Current data therefore support a model in which exercise-induced EVs improve the systemic metabolic and inflammatory milieu and reduce myocardial vulnerability, rather than directly regenerating diabetic myocardium. EV transfer or EV uptake–blocking experiments in diabetic animal models, combined with imaging endpoints such as myocardial strain and extracellular volume, would help establish causality and define therapeutic potential [16,129].

#### 2.5.4 Effects of Exercise-Induced EVs on Viral Myocarditis

In viral myocarditis (VMC), including fulminant myocarditis, direct evidence that exercise-induced EVs drive myocardial recovery remains limited, in part because exercise interventions are rarely feasible during the acute inflammatory phase and clinical trajectories are heterogeneous. Nonetheless, EV profiling studies suggest that circulating EV cargo can reflect myocardial inflammation and may track disease activity. In acute viral myocarditis, plasma exosomal microRNA signatures (e.g., *hsa-miR-548a-3p*, *hsa-miR-500b-5p*) have been reported with diagnostic potential and links to myocarditis-relevant pathways [49]. Pediatric fulminant myocarditis studies similarly describe disease-associated exosomal microRNAs, including inflammatory regulators such as *hsa-miR-146a-5p*, as candidate biomarkers and entry points for immune–cardiac crosstalk [56]. Beyond biomarker work, therapeutic studies indicate that cardiomyocyte-derived large EVs can modulate macrophage polarization and ameliorate myocarditis in experimental settings, supporting a functional role for vesicular signaling in inflammatory resolution [66]. A practical next step is to move from cross-sectional profiling to rehabilitation-phase longitudinal designs to test whether structured post-acute exercise shifts EV profiles toward reparative signatures, and whether these changes correlate with functional recovery or reduced relapse risk [130,131]. Standardized EV pre-analytics and harmonized reporting will be essential for cross-cohort validation and clinical translation [126].

#### 2.5.5 Exercise–EV Signaling as a Mechanistic Bridge in Cardio-Oncology

2.5.5.1 Exercise-Derived EVs as Anticancer Exerkines With Systemic Spillover. Exercise induces coordinated increases in circulating EVs that can function as exerkines, with reported effects on immune and metabolic pathways relevant to cancer biology and cardiovascular resilience. Reviews note that exercise-induced EV cargos (microRNAs, proteins, metabolites) can modulate pathways linked to proliferation, immune surveillance, and metabolic plasticity, offering mechanistic support for clinical observations associating structured activity with improved cancer outcomes and treatment tolerance [132,133]. A recent preclinical study tested exercise-induced plasma EVs directly and reported delayed tumor development with remodeling of the immune tumor microenvironment, supporting the possibility that EVs can act as mediators rather than mere correlates of exercise [134]. Together, these findings motivate the view that exercise-EVs may influence both tumor control and systemic inflammatory/metabolic states that shape cardiovascular vulnerability during cancer care [132,133].

2.5.5.2 CORE as the Clinical Platform: Where EVs Can Add Mechanistic and Biomarker Value. A key challenge in implementing cardio-oncology rehabilitation and exercise (CORE) is the heterogeneity of interventions and endpoints, despite growing recognition of exercise as a preventive strategy for cardiotoxicity [135,136]. The 2025 ICOS-CORE whitepaper proposes research standards and emphasizes the need for mechanistic biomarkers to guide risk stratification and individualized prescriptions [135]. In parallel, JACC: CardioOncology highlights the need for deeper molecular insight into exercise responses in cancer survivors [137]. EVs are of interest in this context because they can be serially sampled and may reflect both tumor-derived and host-response signaling, although their clinical utility remains to be defined [133].

Therapy-related cardiotoxicity and a "pathological EV axis". Evidence that exercise can mitigate anthracycline cardiotoxicity is supported by preclinical and emerging clinical studies, while mechanistic work increasingly highlights EV-mediated tumor–heart crosstalk as an amplifier of injury [138]. In breast cancer models, doxorubicin exposure induced cancer-cell secretion of small EVs that worsened cardiomyocyte injury through regulated cell death pathways, including EV-associated *miR-338-3p*–linked ferroptosis and exosomal *miR-216a-5p*–linked pyroptosis [106,107]. These findings motivate a testable hypothesis for cardio-oncology rehabilitation: exercise-induced EVs may raise the myocardial stress threshold and/or modulate recipient-cell responses to pathological tumor/therapy EVs during chemotherapy. This concept remains under-validated and supports prospective CORE cohorts with early-cycle EV profiling and predefined cardiotoxic endpoints (e.g., GLS decline, hs-cTn rise, CTRCD events) [135,138].

2.5.5.3 ICI-Associated Cardiac Injury: Emerging Evidence for Exercise, With EV Mechanisms Largely Unresolved. Exercise interventions in ICI cardiotoxicity have been minimally studied. A 2025 preclinical study reported that low-intensity exercise performed alongside anti–PD-1 therapy preserved cardiac function and attenuated maladaptive signaling, supporting feasibility and biological plausibility for exercise as an adjunct strategy in ICI settings [139]. However, these data do not directly address extracellular vesicle (EV)–mediated mechanisms, and the molecular pathways linking exercise to cardioprotection under ICI exposure remain largely undefined.

In parallel, EV-based therapeutic strategies have been explored in experimental models of ICI-related myocardial injury. For example, exosomes derived from human bone marrow mesenchymal stem cells (MSC-Exos) were shown to attenuate PD-1/PD-L1 inhibitor–associated cardiac injury [140]. Importantly, these vesicles are exogenously administered and derived from specific cell sources, and therefore should not be considered equivalent to exercise-induced EVs. Rather, they provide proof-of-concept that EV-mediated modulation of immune and inflammatory signaling can influence cardiac outcomes in this context.

Together, the current evidence remains fragmented and does not yet establish a direct mechanistic link between exercise-derived EVs and cardioprotection in ICI-treated settings. In particular, it remains unknown whether structured exercise can reshape circulating EV profiles toward pro-resolving immune signaling in patients receiving ICIs, or whether such changes precede or predict reduced cardiac risk beyond conventional surveillance strategies [135,139].

Systemic factors common in oncology populations may further modify EV signaling and exercise responsiveness. Cancer cachexia and tumor–adipose crosstalk generate a chronic inflammatory and metabolically adverse milieu that can lower myocardial stress tolerance even before cardiotoxic therapies are initiated. Reviews identify EVs as central messengers in cachexia, carrying nucleic acids and proteins that drive adipose and skeletal muscle wasting and broader metabolic imbalance [141,142]. From a cardio-oncology perspective, such EV-mediated systemic remodeling may influence baseline cardiac vulnerability and potentially alter responsiveness to exercise interventions.

In therapy-related cardiomyopathy more broadly—particularly anthracycline- and ICI-associated injury—exercise is increasingly recognized as cardioprotective, although the contribution of EV-mediated mechanisms remains insufficiently defined. Exercise training mitigates anthracycline-associated declines in cardiac function, oxidative stress, and mitochondrial injury, providing a clinical rationale for exercise-based cardio-oncology rehabilitation programs [143]. In contrast, a growing body of literature implicates therapy- or tumor-derived EVs in amplifying cardiotoxicity through inflammatory signaling and regulated cell-death programs [106]. Whether exercise-induced EVs can counterbalance these pathogenic signals or reprogram myocardial responses during cancer therapy remains speculative at present.

There is currently no direct evidence linking exercise-induced EVs to cardioprotection in ICI-associated myocarditis. Specifically, studies employing EV transfer or blockade approaches in ICI models are lacking, and prospective clinical investigations integrating structured exercise interventions with longitudinal EV profiling have not yet been performed. Addressing these gaps will be essential to determine whether EV signatures provide incremental predictive value for cardiotoxic events or myocardial resilience beyond established biomarkers [16,87].

## 3. Conclusions

Extracellular vesicles are increasingly recognized as active participants in myocardial injury and repair, rather than passive byproducts or static biomarkers. Across ischemic heart disease, viral myocarditis, metabolic cardiomyopathies, and cardio-oncology, EV-mediated signal-

ing shows clear context- and stage-dependence, influencing acute stress responses, post-injury repair, and long-term remodeling through coordinated effects on immune, metabolic, vascular, and stromal pathways. These shared EV-driven mechanisms help explain why diverse cardiac insults often converge on similar patterns of myocardial dysfunction and recovery.

Exercise represents a particularly powerful physiological modulator of EV biology. Exercise-responsive exosomes act as systemic exerkines that favor adaptive repair by promoting metabolic homeostasis and inflammatory resolution, offering a mechanistic basis for the benefits of cardiac rehabilitation beyond traditional hemodynamic effects. In cardio-oncology, exercise–EV interactions further suggest a link between anticancer benefits and cardioprotection, which may be especially relevant for immune checkpoint inhibitor–associated cardiac injury, a setting where early biomarkers and preventive strategies remain limited.

Despite substantial progress, several barriers must be overcome before EV-based approaches can be translated into routine clinical practice. Key challenges include defining disease- and stage-specific EV cargos, addressing heterogeneity among EV populations, standardizing isolation and quantification methods, and establishing causal relationships in human studies. In parallel, the clinical application of EV biomarkers and therapies will need to be integrated with existing rehabilitation strategies, particularly structured exercise programs, to ensure feasibility and impact.

In conclusion, EV-centered signaling offers a unifying lens through which myocardial injury across etiologies can be understood and potentially modified. Integrating EV biology with exercise science, systems-level approaches, and well-designed clinical studies will be critical for translating these insights into practical tools for precision cardiovascular medicine and cardio-oncology rehabilitation.

## Author Contributions

ZL conceived and designed the review. CH and LC contributed substantially to the analysis, interpretation, and synthesis of the published literature and drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

The authors declare no conflicts of interest.

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During the preparation of this work the authors used ChatGPT-5.2 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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