The Eurasian Journal of Life Sciences 2025; 1 (2): 25-35

journal homepage: https://www.eajls.com
https://doi.org/10.47093/3033-5493.2025.1.2.25-35

REVIEW

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Informed consent statement: Not required.

Funding: The study was not sponsored (own resources).

Competing interests: The authors declare no conflict of interest.

Ethical approval: Not required.

Data sharing: Not applicable.

Acknowledgments: The authors would like to express their gratitude to Mr. Yang Baofeng, President of Harbin Medical University, and Professor Yanan Jiang for the opportunity to discuss and collaborate on a research project on extracellular vesicles and their impact on the development of chronic heart failure.

Manuscript source: Unsolicited manuscript.

Country/territory of origin: Russia, China

Extracellular vesicles in the heart failure pathogenesis: mechanisms and therapeutic potential

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ABSTRACT

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, necessitating a deeper understanding of its molecular mechanisms. Extracellular vesicles (EVs) — exosomes, microvesicles, and apoptotic bodies and less-studied subtypes – have emerged as key intercellular communication

Received: 11.07.2025

Accepted: 21.10.2025

Date of publication: 26.12.2025

mediators in cardiovascular diseases. These nanosized particles carry bioactive molecules such as proteins, lipids, and nucleic acids, influencing processes including cardiac remodeling, inflammation, fibrosis, and angiogenesis.

EVs derived from cardiomyocytes, endothelial cells, fibroblasts, and immune cells contribute to HF progression by modulating pathological signaling pathways. For instance, cardiomyocyte-derived EVs may propagate hypertrophy and apoptosis, while fibroblast-derived EVs promote extracellular matrix deposition, leading myocardial stiffness. Conversely, certain EV subpopulations exhibit cardioprotective effects, underscoring their dual role in HF pathogenesis. This review summarizes current knowledge on EV biogenesis, composition, and function in HF, highlighting their diagnostic and therapeutic potential.

We discuss emerging evidence from preclinical and clinical studies, focusing on EV-based biomarkers for early diagnosis and prognosis of HF. Furthermore, we explore therapeutic applications of engineered EVs for targeted drug delivery. Despite considerable advances, unresolved issues such as EV heterogeneity, a lack of standardization isolation methods, and difficulties in applying the results in practice. Addressing these challenges is crucial for unlocking novel strategies for HF management. Integration of fundamental and clinical findings was used to analyze the role of EVs in HF and to evaluate their potential for novel diagnostic and therapeutic applications.

Key Words: biomarker; fibrosis; inflammation; non-coding RNAs; microRNAs; lncRNAs; drug delivery systems

Citation: Tokmachev RE, Antakova LN, Esaulenko IE, Shishkina VV, Pulver AYu, Gerasimova OA, Jiang Y. Extracellular vesicles in the heart failure pathogenesis: mechanisms and therapeutic potential. *The Eurasian Journal of Life Sciences.* 2025;1(2):25-35. https://doi.org/10.47093/3033-5493.2025.1.2.25-35

Introduction

Heart failure (HF) is a major global health challenge, affecting over 26 million people worldwide and contributing significantly to cardiovascular morbidity and mortality [1]. Projections are even more alarming, however, with total costs expected to increase by 127 % between 2012 and 2030 [1]. It is characterized by the heart's inability to pump blood efficiently, leading to systemic complications and reduced quality of life. Despite advances in treatment, prognosis remains poor, with a 5-year survival rate of approximately 50% [2]. The economic burden is substantial, with HF-related hospitalizations accounting for a significant portion of healthcare expenditures [3]. Given the limited efficacy of current therapies, there is a pressing need to explore novel molecular mechanisms underlying HF progression, particularly the extracellular vesicles (EV) role. Circulating EV-miRNAs (microRNAs), particularly those in extracellular vesicles, serve as biomarkers for early diagnosis, poor prognosis, and therapeutic targets in HF patients [4]. EV for diagnosing HF can be isolated from different biological fluids: plasma, serum, saliva. Existing methods for diagnosing heart failure such as echocardiography and N-terminal pro-B-type natriuretic peptide testing are the "gold standard" and provide complementary information, each playing a distinct role, serve complementary purposes. EV offer fundamentally new capabilities that these methods do not cover. Echocardiography reveals structural and functional changes that have already occurred. N-terminal pro-B-type natriuretic peptide levels increase in response to active cardiac overload. EVs, on the other hand, can serve as a signal of cellular stress and damage at the earliest stages, even before changes become visible on ultrasound or lead

to a massive release of natriuretic peptides. Research into biomarkers based on EVs is actively underway in relation to disease development, with some approaches already in advanced stages of testing. Oncology remains a leader in the clinical development of EV biomarkers, largely due to the urgent need for non-invasive monitoring methods (liquid biopsy), as well as neurological and infectious diseases [5].

Specific EV-miRNAs, such as miR-92-5p, miR-146a, miR-181c, and miR-495, demonstrate significant diagnostic value for HF, while EV-enriched miRNAs like miR-192, miR-34a, miR-425, and miR-744 are potential prognostic markers. Notably, miR-30d-5p and miR-126a-5p exhibit unique biomarker characteristics in diabetic patients with heart failure with preserved ejection fraction (HFpEF), showing coordinated downregulation in circulating EVs and myocardial tissues, inversely correlating with reduced cardiac output [6].

Hypoxia enhances cardiomyocyte uptake of EVs. Adipose-derived regenerative cell exosomes are enriched with anti-apoptotic miRNAs, among which miR-214 is the most abundant. Silencing miR-214 in adipose-derived regenerative cell significantly diminished the anti-apoptotic effects of their EV on cardiomyocytes [7].

Definition of extracellular vesicles and their role in intercellular communication in the heart

EV are membrane-bound nanoparticles released by virtually all cell types, playing crucial roles in intercellular communication [8]. They are broadly classified into three main subtypes: exosomes (30–150 nm), formed within multivesicular bodies and released upon their fusion with the plasma membrane; ectosomes (microvesicles) (100–1000 nm), generated through outward budding of the plasma membrane; apoptotic bodies (1–10 μm), produced during programmed cell death [9].

Other less-studied EV populations include oncosomes and large oncosomes [10], though their relevance in HF remains unclear. Exosome biogenesis is regulated by ESCRT (endosomal sorting complexes required for transport)-dependent and -independent pathways, with key involvement of tetraspanins (CD63, CD81) and lipids [11].

EVs facilitate crosstalk between cardiac cells (cardiomyocytes, fibroblasts, endothelial cells) and immune cells by transferring bioactive cargo, including proteins (e.g., heat shock proteins), lipids (e.g., sphingomyelin), and nucleic acids (e.g., microRNAs) [12]. For example, cardiomyocyte-derived EVs enriched in miR-208a exacerbate hypertrophy in recipient cells [13], while endothelial EVs modulate angiogenesis via vascular endothelial growth factor (VEGF) signaling [14]. Dysregulated EVs signaling contributes to pathological remodeling in HF, making them promising therapeutic targets [15]. EVs take part in cardiac physiology and pathophysiology.

EVs play a crucial role in maintaining cardiac homeostasis by facilitating intercellular communication under normal physiological conditions. Cardiomyocytes, endothelial cells, and cardiac fibroblasts constitutively release EVs that contribute to three major processes:

- Tissue repair: EVs derived from cardiac progenitor cells promote cardiomyocyte survival and angiogenesis via transfer of pro-survival miRNAs (miR-210 and miR-132) [16].
- Metabolic regulation: Endothelial-derived EVs transport glycolytic enzymes to cardiomyocytes, optimizing energy supply in response to stress [17].

- Immune modulation: EVs from healthy cardiomyocytes suppress excessive inflammation by carrying anti-inflammatory cytokines [18].

These physiological functions are disrupted in HF, where EVs composition and release dynamics are altered, shifting their role from protective to pathological (Table 1).

Table 1. Extracellular vesicle-mediated signaling in the pathogenesis of heart failure

Process	Effects	Explanations	References
Inflammation	Pro-inflammatory EV cargo	Activated macrophages release EVs containing TNF-α and IL-6, exacerbating myocardial inflammation	[19]
	NLRP3 inflammasome activation	Cardiomyocyte-derived EVs deliver inflammasome components (ASC, caspase-1), amplifying pyroptosis in HF	[20]
Fibrosis	Fibroblast activation	Cardiac fibroblast-derived EVs enriched in TGF-β1 and miR-21-5p drive collagen deposition, promoting stiffening of the ECM	[21]
	MMP secretion	Endothelial-derived EVs stimulate MMP-2 and MMP-9 production, accelerating ECM degradation and adverse remodeling	[22]
Hypertrophy	Pro-hypertrophic miRNAs	Cardiomyocyte-derived EVs transfer miR-199a and miR-208a to neighboring cells, activating mTOR pathways, which play a central regulator role of cell growth, proliferation, survival, and autophagy, the process of degradation of damaged cellular components.	[23]
	Paracrine signaling: promoting hypertrophic responses	EVs from pressure-overloaded hearts carry AT1R	[24]
Apoptosis	Mitochondrial dysfunction	EV from ischemic cardiomyocytes contain mitochondrial DNA ragments, triggering apoptosis in recipient cells	[25]

Note: ASC — apoptosis-associated speck-like protein; AT1R — angiotensin II type 1 receptors; ECM — extracellular matrix; EVs — extracellular vesicles; HF — heart failture; IL-6 — Interleukin-6; miR / miRNAs — microRNAs; MMP — matrix metalloproteinase; mTOR — mammalian target of rapamycin; NLRP3 — Nucleotide-binding oligomerization domain-, Leucine-Rich Repeat-, and Pyrin domain-containing protein 3; TGF-β1 — Transforming growth factor β 1; TNF-α — tumor necrosis factor α.

EVs in HF originate from multiple cardiac cell types, each contributing distinct cargo that influences disease progression. Below, we summarize the key cellular sources and their pathological or protective roles.

Cardiomyocytes release EVs that play dual roles in HF, depending on the cellular states. Their pathological effects are mediated by hypertrophy and apoptosis [24, 26]. EVs from stressed cardiomyocytes contain miR-208a and miR-199a, which activate hypertrophic pathways in neighboring cells [24]. Ischemic cardiomyocytes release EVs carrying mitochondrial DNA and caspase-3, promoting cell death [27]. At the same time EVs also have protective effects. One from preconditioned cardiomyocytes deliver heat shock protein 70 (HSP70) and miR-24, reducing infarct size (Table 2) [28].

Endothelial-derived EVs regulate vascular function and inflammation in HF. EVs from dysfunctional endothelium carry TGF-β and miR-17-92, promoting fibroblast activation and fibrosis [14]. In ischemic myocardium pro-angiogenic EVs transport VEGF and miR-126. One promoted angiogenesis during MI by

Table 2. Pathological and protective extracellular vesicles subsets in heart failure

Extracellular vesicles subset	Cargo signature	Functional role in heart failure	Effect	References
Cardiomyocyte-EVs	miR-208a, caspase-3	Promotes hypertrophy and apoptosis	Pathological	[24, 26]
Cardiomyocyte-EVs	miR-24, HSP70,	Reduces infarct size and enhances repair	Protective	[28]
Cardiomyocyte-EVs	miR-30d	Inhibits profibrotic pathways in the myocardium and prevents α-SMA upregulation	Protective	[29]
Cardiomyocyte-EVs	miR-221	Alleviates fibrosis, suppresses apoptosis, and improves post-myocardial infarction cardiac function	Protective	[30]
Macrophage-EVs	TNF-α, NLRP3	Promotes inflammation	Pathological	[20]
Fibroblast-EVs	miR-21, TGF-β1	Drives fibrosis and extracellular matrix remodeling	Pathological	[21]
Endothelial-EVs	miR-126, VEGF	Stimulates angiogenesis	Protective	[143]

Note: EVs — extracellular vesicles; HSP70 — heat shock protein 70; IL-6 — Interleukin-6; miR — microRNAs; NLRP3 — Nucleotide-binding oligomerization domain-, Leucine-Rich Repeat-, and Pyrin domain-containing protein 3; TGF-β1 — Transforming growth factor β 1; TNF-α — tumor necrosis factor α; VEGF — vascular endothelial growth factor; α-SMA — α-smooth muscle actin.

upregulating VEGF and CD34 expression and endothelial cell tube formation and migration via HIF-1α [31]. Macrophage-derived EVs containing TNF-α and Nucleotide-binding oligomerization domain-, Leucine-Rich Repeat-, and Pyrin domain-containing protein 3 (NLRP3) components exacerbate myocardial inflammation [20]. However, regulatory T-cell-derived EVs suppress excessive immune responses by delivering IL-10 and miR-146a [18].

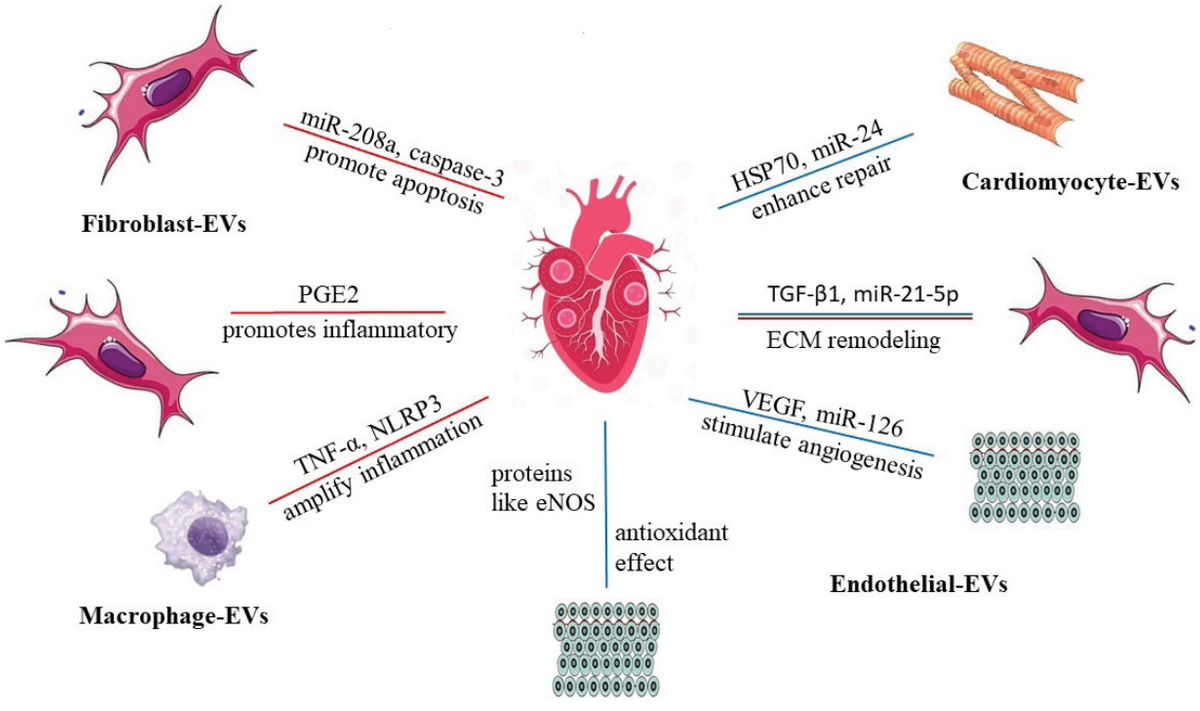
Extracellular vesicles cargo and functional implications in heart failure

EVs carry functional proteins that regulate cardiac signaling. Specifically, TGF-β1 promotes fibrosis [32] and NLRP3 inflammasome components from macrophage-derived EVs trigger inflammation [20]. Conversely, protective functions are mediated by HSP70 from cardiomyocyte-derived EVs enhances cell survival [28] and endothelial microparticles carry protective proteins like functional eNOS (endothelial nitric oxide synthase 3) [29]. The latter counteract oxidative stress by restoring NO balance and reducing reactive oxygen species via the eNOS/Akt (protein kinase B) pathway under lipotoxic conditions, though they may have opposing roles in homeostasis [33].

Prostaglandin E2 (PGE2) carried by fibroblast-derived EVs promotes inflammatory signaling through prostaglandin E receptors (EP) 1/EP3 while paradoxically offering protective effects via EP2/EP4-mediated suppression of myofibroblast activation and collagen production, depending on the microenvironment [34]. The dual role of EVs-associated PGE2 highlights its complex involvement in fibrosis progression and resolution, with therapeutic potential emerging through modulation of 15-PGDH (15-hydroxyprostaglandin dehydrogenase) activity and cAMP-dependent pathways. EVs-containing PGE2 is being investigated for targeted delivery of antifibrotic agents such as COX-2 (cyclooxygenase-2) inhibitor [34].

Sphingomyelin and cholesterol stabilize EVs structure and modulate membrane fusion [35]. EV-enriched miRNAs and long non-coding RNAs are key regulators of HF. The pathological group of miRNAs involves miR-21 (fibroblast-derived EVs and leads to the development of fibrosis) [20] and miR-208a (cardiomyocyte EVs, leads to the development of hypertrophy) [23]. Another group of miRNAs mediates cardioprotective effect and represent by miR-126 (endothelial-derived EVs participate in the angiogenesis) [31] and miR-146a (regulatory T-cells-derived EVs and provides anti-inflammatory effects) (Fig.) [18].

FIG. Extracellular vesicles' activation mechanisms in heart failure pathogenesis



Note: blue line — EV's protective effect, red — EV's pathological effect. ECM — extracellular matrix; eNOS — endothelial nitric oxide synthase 3; EVs — extracellular vesicles; HSP70 — heat shock protein 70; miR — microRNAs; NLRP3 — Nucleotide-binding oligomerization domain-, Leucine-Rich Repeat-, and Pyrin domain-containing protein 3; PGE2 — Prostaglandin E2; TGF-β1 — Transforming growth factor β 1; TNF-α — tumor necrosis factor α; VEGF — vascular endothelial growth factor.

Besides, EVs-loaded miR-126 significantly attenuated myocardial ischemia-reperfusion injury and enhanced cardiac function in rats [36].

EVs from atorvastatin-pretreated bone marrow mesenchymal stem cells exhibited elevated miR-139-3p levels, which promoted macrophage polarization and post-myocardial infarction (MI) cardiac repair by inhibiting the Stat1 pathway [37].

Nicotinamide mononucleotide-pretreated mesenchymal stem cell EVs showed increased miR-210-3p expression, enhancing angiogenesis and improving post-MI outcomes via targeting EFNA3 (Ephrin A3) [38]. EVs from adipose-derived stem cells conferred cardioprotective effects in post-MI, with miR-221-overexpressing adipose-derived stem cells EVs markedly suppressing apoptosis and improving cardiac function [30].

Extracellular vesicles as biomarkers in heart failure

EVs have emerged as promising biomarkers for HF due to their cell-specific cargo and stability in circulation. Their diagnostic and prognostic potential is being actively explored in clinical studies, particularly through liquid biopsy approaches.

Diagnostic Biomarkers:

- Cardiomyocyte-derived EVs contain elevated levels of cardiac troponin I and EVs correlate with myocardial injury severity [40], and also miR-1 and miR-133a in EVs show high specificity for acute HF [39, 41].
- Fibroblast-derived EVs enriched with CD81 and Flotilin-1, serve as natural nanocarriers for targeted antifibrotic drug delivery to fibrotic heart and lung tissues, improving therapeutic efficacy while reducing off-target effects [42]. These EVs accumulate in fibrotic areas via membrane-specific trafficking and can be loaded with antifibrotic agents like TGF-β signaling pathway inhibitors. This offers a precision medicine approach for treating cardiac and pulmonary fibrosis [42].

Prognostic Biomarkers:

- Circulating levels of miR-17, miR-126-3p, and some blood parameters, including neutrophil to lymphocyte ratio, were significantly associated with mortality in cardiovascular multimorbidity patients [43].
- Inflammatory EVs including and NLRP3s associate with progressive ventricular remodeling post-myocardial infarction [20].
- MiR-17-5p, miR-20a-5p, miR-21, miR-23, miR-27, miR-210, miR-221, and miR-106b-5p) associated with HF incidence [44].

Therapeutic applications of extracellular vesicles

EVs have cardioprotective potential. So, EVs derived from specific cell types exhibit intrinsic therapeutic properties. Mesenchymal Stem cell-derived EVs deliver anti-apoptotic miRNAs such as miR-21-3p to ischemic myocardium, thereby reducing inflammation and promoting angiogenesis [38]. EVs derived from cardiospheres suppress fibrosis in HFpEF by inhibiting TGF-β1/Smad3 signaling [21].

EVs can be bioengineered to enhances their therapeutic precision. EVs with surface modification improve homing to damaged myocardium [45]. EVs can be applied as drug delivery vehicles with advantages over synthetic nanoparticles. These include natural targeting, exactly endothelial EVs home to inflamed vasculature via integrin αvβ3, bypassing systemic clearance [38] and lower toxicity, because EVs show reduced immunogenicity compared to PEGylated liposomes, minimizing adverse immune reactions [47].

These examples illustrate 4 EVs therapeutic cargo examples: anti-fibrotic, anti-inflammatory, pro-angiogenic, anti-hypertrophic.

Future perspectives and unresolved issues

Unmodified EVs are rapidly cleared by the liver/spleen; PEGylation extends circulation but reduces targeting efficiency [48].

However, the field faces significant challenges in standardizing EV production. There is no consensus on isolation methods such as ultracentrifugation vs. size-exclusion chromatography or dosing metrics such as particle count vs. protein content [48].

Potential risks include the prolonged suppression of miR-21 (in anti-fibrotic therapies) may impair wound healing or promote tumorigenesis [49, 50].

Engineered bone marrow mesenchymal stem cell-derived EVs, modified with cardiomyocyte-targeting peptides to deliver miR-302, improved cardiac function after ischemia-reperfusion injury by reducing apoptosis, inflammation, and infarct size [51].

Roadmap for clinical implementation

- Short-Term (0–5 years): Validate EV biomarkers. Optimize isolation protocols for clinical-grade EVs.
- Mid-Term (5–10 years): Develop hybrid EVs combining synthetic lipids with natural membranes to balance scalability and bioactivity [52].
- Long-Term (10+ years): Engineer EVs with hypoxia-responsive cargo release for ischemic heart disease [53]. Deploy AI-driven platforms for dynamic EV dosing based on real-time biomarker feedback [54]. Create fully synthetic “designer EVs” with tunable properties [55].

Conclusion

The study of EVs in heart failure has transformed our understanding of intercellular communication in the diseased heart. What began as basic observations about membrane-bound particles has matured into a sophisticated recognition of EVs as central players in cardiac remodeling, offering unprecedented diagnostic and therapeutic opportunities. The past decade has revealed how specific EV subpopulations drive pathological processes — whether through miR-331-5p-mediated fibrosis, NLRP3-containing vesicles amplifying inflammation, or metabolic regulators like tRF-Tyr-GTA-010 influencing calcium handling. Simultaneously, the therapeutic potential of EVs has moved beyond theoretical promise to concrete applications, with engineered vesicles now demonstrating targeted delivery and reproducible effects in preclinical models.

Despite this progress, the field faces crucial challenges that must be addressed to realize clinical potential. Standardization remains the foremost obstacle, as variations in isolation techniques and characterization methods continue to hinder reproducibility across studies. The biological complexity of EVs — their heterogeneous cargo, dynamic release patterns, and context-dependent effects — presents both an opportunity for precision medicine and a challenge for consistent therapeutic development. Current clinical trials are beginning to bridge this gap, particularly in exploring mesenchymal stem cell-derived vesicles for post-infarct repair, while emerging technologies like microfluidic sorting and artificial intelligence-based profiling promise to overcome existing limitations in EV characterization and targeting.

But today’s methods for isolating and characterizing EVs (ultracentrifugation, NTA, flow cytometry) truly require expensive equipment, highly qualified specialists, and a lengthy process. This is the domain of large research centers. As technologies become simpler and cheaper, the method will become more accessible.

Looking ahead, the coming years will likely see EV-based approaches transition from research tools to clinical assets. Diagnostic applications may reach clinical practice first, given the strong biomarker data already accumulated, while therapeutic implementations will require more extensive safety and efficacy testing. The ultimate goal remains the development of personalized EV therapies

tailored to individual patients' disease profiles — an ambition that now appears increasingly attainable. As research continues to unravel the complexities of EV biology in heart failure, these remarkable nanoparticles are poised to transform how we diagnose, monitor, and treat this devastating condition, potentially ushering in a new era of cardiovascular medicine.

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