

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT  
AND TRANSPLANTMicrocurrent Therapy in Cardiac Repair: Bridging  
Mechanistic Biology and Clinical Evidence

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**ABSTRACT:** Cardiovascular disease remains a major cause of morbidity and mortality, with heart failure representing the common and often irreversible end stage, for which current therapies are largely palliative rather than restorative. Cardiac microcurrent therapy delivers a low-intensity, nondepolarizing direct current across the myocardium and has been proposed to modulate fibrosis, inflammation, and remodeling in heart failure with reduced ejection fraction. In Cardiac Microcurrent I (New York Heart Association III nonischemic heart failure with reduced ejection fraction), left ventricular ejection fraction increased by 12.6% at 6 months, 6-minute walk distance improved by 191 m, and 8 of 10 patients improved to New York Heart Association I within 2 weeks. In the randomized Cardiac Microcurrent II trial, patients showed further improvements, including a 5.1% increase in left ventricular ejection fraction, a reduction in New York Heart Association class (up to 69%), and a 38 m increase in 6-minute walk distance. However, NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels did not show a consistent corresponding reduction. In vitro, microcurrent altered the myofibroblast phenotype and reduced the expression of transforming growth factor- $\beta$ 1, collagen,  $\alpha$ -smooth muscle actin, and fibronectin. Transcriptomics revealed downregulation of inflammatory and immune pathways, while cardiomyocytes from spontaneously hypertensive rats exhibited enhanced survival and stress resistance. This review combines early clinical observations and preclinical findings to examine potential mechanisms of action and bioelectrical effects of cardiac microcurrent therapy. Given the limited clinical evidence and largely in vitro nature of the data, the current mechanistic findings should be considered preliminary. We highlight key knowledge gaps and propose future studies to define molecular mechanisms, discover biomarkers, analyze key signaling pathways, and evaluate clinical outcomes in adequately powered, sham-controlled trials, which could further validate this therapeutic approach.

**Key Words:** animals ■ inflammation ■ morbidity ■ phenotype ■ stroke volume

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, with heart failure representing the common end stage of many cardiac pathologies. A central limitation in recovery is the heart's limited regenerative capacity, along with maladaptive, adverse remodeling of the myocardium.<sup>1</sup> Myocardial injury triggers fibroblast activation and a fibrotic response characterized by excessive accumulation of activated myofibroblasts and deposition of extracellular matrix (ECM), leading to increased myocardial stiffness, adverse remodeling, and progressive

structural and functional decline.<sup>2–8</sup> Although initially reparative, this process ultimately contributes to heart failure progression.

For decades, researchers and clinicians have sought strategies to preserve viable myocardium, slow the progression of fibrosis, and promote tissue repair. Yet, despite major advances in pharmacology, device technology, and cell-based therapies, current therapies remain insufficient in directly targeting myofibroblast activation and fibrosis, highlighting a critical unmet need for novel therapeutic approaches that can address the underlying

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Nonstandard Abbreviations and Acronyms

|              |                                              |
|--------------|----------------------------------------------|
| <b>C-MIC</b> | cardiac microcurrent                         |
| <b>ES</b>    | electric stimulation                         |
| <b>ECM</b>   | extracellular matrix                         |
| <b>HFrEF</b> | heart failure with reduced ejection fraction |
| <b>LVEF</b>  | left ventricular ejection fraction           |
| <b>NYHA</b>  | New York Heart Association                   |

mechanisms of adverse remodeling and heart failure progression.

Microcurrent therapy is a bioelectrical approach that uses low-intensity, nondepolarizing currents and has been applied in wound healing and sports medicine. More recently, implantable microcurrent devices have marked a new era of bioelectronic medicine, extending their potential into cardiovascular applications.<sup>9–11</sup> Early clinical data from patients with heart failure suggest functional improvement beyond simple pacing or resynchronization.<sup>12</sup> The transition from surgical epicardial to less-invasive subcutaneous delivery further expands its translational potential, highlighting the critical need for a deeper understanding of the underlying cellular and molecular mechanisms.

This review broadly provides an overview of evidence across clinical and experimental domains to:

- Summarize findings from clinical trials and emerging data from the cardiac microcurrent (C-MIC) therapy program.
- Evaluate in vitro and in vivo effects of microcurrent on cardiomyocytes and myofibroblasts.
- Present emerging hypotheses on the mechanisms by which microcurrent influences fibrosis, cardiac remodeling, and overall cardiac function.
- Bridge clinical observations with existing molecular insights to address a critical gap in the current literature.

LITERATURE SEARCH AND REVIEW  
METHODOLOGY

We aimed to identify both clinical and experimental studies examining the application of electrical stimulation (ES) for cardiac repair, cellular modulation, and functional improvement. We used 2 primary search strategies using the PubMed database, covering literature published up to December 2025:

1. (“cardiac stimulation” OR “electrical stimulation” OR microcurrent) AND (“cardiomyocytes” OR “cardiac cell” OR “heart cell” OR myocytes)
2. (“electrical stimulation” OR “cardiac stimulation” OR microcurrent) AND (“heart tissue” OR “cardiovascular” OR “LVEF” OR “cardiac function” OR

“LVED” OR “NYHA” OR “myocytes” OR “cardiac cell”) NOT (nerve OR brain OR cranial OR wound OR bone)

These searches were designed to capture preclinical, translational, and clinical studies investigating the effects of electrical stimulation on cardiac cell behavior and therapeutic potential in heart failure. Key outcomes of interest included effects on cell proliferation, differentiation, electrophysiology, fibrosis, contractility, and remodeling, as well as functional end points such as left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and survival.

To ensure relevance, studies on noncardiac applications (eg, nervous system, cranial tissues, bone) were excluded. Titles and abstracts were manually screened to retain studies examining the effects of electrical or microcurrent stimulation on cardiac tissue, particularly those that provided mechanistic insights, and the reference lists of relevant reviews were examined to identify additional studies.

Microcurrent Therapy: An Overview

The concept of bioelectricity dates back centuries. Luigi Galvani first demonstrated that ES could induce muscle contractions in frog legs, marking the discovery of endogenous electrical signaling in biology.<sup>13</sup> Endogenous bioelectric signals, generated by ion gradients across cell membranes, are not just signs of metabolism but also serve as endogenous cues that regulate biological processes<sup>14</sup> and play essential roles in tissue repair,<sup>15–17</sup> embryonic development,<sup>18</sup> stem cell differentiation,<sup>19,20</sup> and cell migration,<sup>19,21</sup> among other functions.

Electrical stimulation is widely used in regenerative medicine and tissue engineering, involving modalities like Transcutaneous Electrical Nerve Stimulation, Electrical Muscle Stimulation, Functional ES, and microcurrent-based approaches.<sup>22</sup> Across neural regeneration, bone repair, and wound healing, ES has consistently demonstrated its capacity to guide complex tissue repair processes.<sup>23–26</sup>

Microcurrent therapy represents a distinct form of bioelectric medicine that operates in the milliamperage range, significantly lower than those used in cardiac pacing, cardiac resynchronization therapy, or cardiac contractility modulation, which trigger myocardial contractions, terminate arrhythmias, or depolarize the cell membrane through continuous electrical impulses.

In the heart, cardiac remodeling from cellular pathology involves myocyte hypertrophy, necrosis, apoptosis, collagen accumulation, and fibrosis, among other processes. These changes are partly influenced by endogenous electric fields, especially injury currents resulting from cell membrane disruption.<sup>27–29</sup> Given that cells inherently generate and respond to biological electrical

signals, microcurrent treatment may serve to modulate this endogenous electrical activity to promote repair and regeneration.<sup>30</sup>

Collectively, existing studies indicate that microcurrent therapy exerts biologically meaningful effects across a wide range of tissues and cell types. A better understanding of its mechanisms could expand its use in the treatment of more cardiovascular disease states.

## C-MIC Trial Outcomes and Observations

C-MIC therapy delivers ultra-low-amplitude direct currents through an implanted system, consisting of intracardiac leads, a power source, and an external Programming and Uploading Tool (Figure 1). It has been assessed in a series of early-phase studies in patients with heart failure with reduced ejection fraction (HFrEF).

In the first-in-human C-MIC I pilot study, patients ( $n=10$ ) with chronic nonischemic dilated cardiomyopathy and refractory NYHA class III symptoms received C-MIC therapy.<sup>10</sup> The procedure was safe and feasible, with no device-related adverse events. Within 6 months, patients experienced significant improvements in LVEF, 6-minute walk distance, NYHA class, and quality of life, with 8 of 10 patients improving to NYHA class I as early as 2 weeks post-implantation. The C-MIC I long-term study evaluated the durability of these effects in 7 patients for up to 2 years after initial therapy, with deactivation at 6 months. Improvements in LVEF (+12.6%,  $P=0.002$ ), 6-minute walk distance (+191 meters;  $P<0.0001$ ), NYHA class, and SF-36 quality-of-life scores were sustained over the entire follow-up period, with no device-related adverse events and only 1 noncardiac death.<sup>31</sup> These findings suggest a durable therapeutic effect even after therapy is discontinued.

The randomized, controlled, open-label C-MIC II trial ( $n=70$ ) confirmed these findings.<sup>32</sup> At 6 months, C-MIC therapy led to significantly greater improvements in LVEF (mean difference, +5.1%;  $P<0.001$ ), functional class (69% improved by  $\geq 1$  NYHA class;  $P<0.001$ ), KCCQ quality-of-life score (60% with  $\geq 5$ -point improvement;  $P<0.001$ ), and 6-minute walk distance (38% with  $\geq 30\%$  increase;  $P=0.002$ ) compared with controls.<sup>32</sup> Collectively, available clinical data suggest safety and sustained functional improvements (6–24 months) in nonischemic HFrEF.<sup>31,32</sup>

Biomarker analyses from the trials reveal a complex picture. NT-proBNP did not show a significant reduction at 6 months, despite functional improvement, although patients exhibited an early transient rise followed by a gradual decline.<sup>32</sup> This suggests that the mechanisms underlying the observed benefits may not be fully captured by conventional biomarkers of myocardial stress, or that the relationship between microcurrent therapy, myocardial remodeling, and biomarker responses remains incompletely understood. This observation is

further supported by the relatively modest changes in LV end-diastolic diameter observed at 6 months, which may indicate that the early clinical benefits are not solely attributable to rapid reductions in ventricular wall stress. In addition, it remains unknown whether microcurrent therapy directly influences the synthesis, secretion, or clearance of natriuretic peptides, which could further complicate the interpretation of NT-proBNP responses. Furthermore, the study lacked sufficient power to rule out significant changes in this biomarker. Additional analyses from the C-MIC II trial data and its ongoing follow-up studies will evaluate the correlation between changes in NT-proBNP and structural remodeling.

Long-term echocardiography data indicate progressive and sustained improvements in cardiac function and structure up to 24 months after stopping C-MIC therapy.<sup>10,31,32</sup> Whether these changes overlap with classical reverse remodeling or represent a distinct bioelectric-driven remodeling process remains an open question. C-MIC preclinical work links electrical field changes to edema dysfunction, suggesting that edema resolution may contribute to much of the benefit.<sup>32,33</sup>

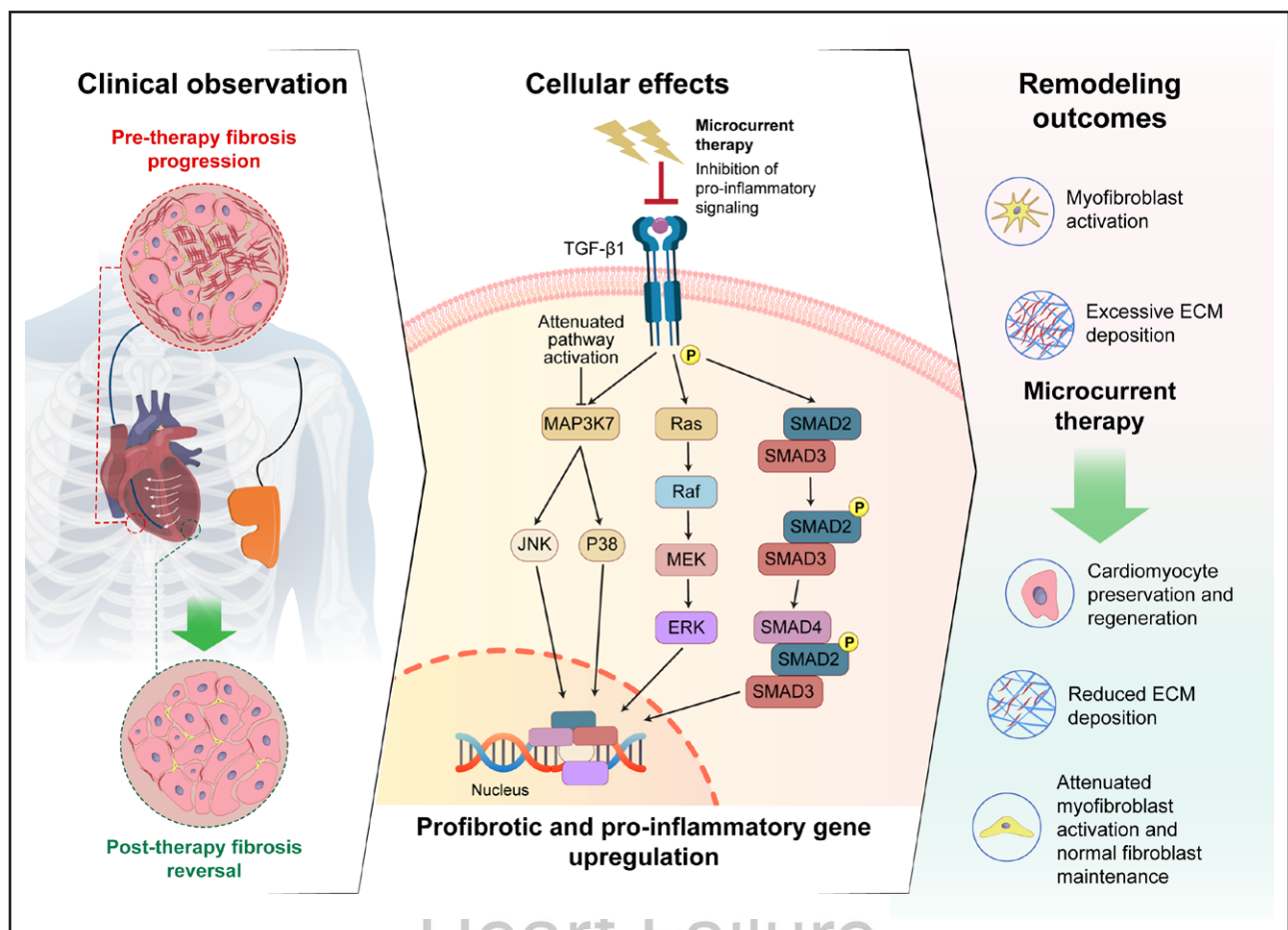
Current clinical evidence is limited by study design. C-MIC I was a single-arm pilot study without a control group and was primarily designed to assess safety and feasibility while providing preliminary evidence of potential clinical benefit. C-MIC II was an open-label, randomized controlled trial without blinding or a sham control, limiting the ability to fully exclude placebo effects, observer bias, and other sources of performance bias. In addition, both studies enrolled patients with nonischemic HFrEF, which may limit the generalizability of the findings to other heart failure populations, including those with ischemic cardiomyopathy, HFmrEF, heart failure with preserved ejection fraction, or less advanced disease stages.

## Observed Cellular and Physiological Effects

Although the aforementioned clinical outcomes are encouraging, mechanistic in vitro studies are essential to define how microcurrent stimulation influences cardiac cells and remodeling processes.

To elucidate the biological effects of microcurrent therapy, simplified in vitro microcurrent platforms were developed to deliver controlled direct electrical currents to cultured cells.<sup>34</sup> Initial studies showed reproducible, cell-specific effects of microcurrent, especially in cardiac myofibroblasts and cardiomyocytes. Treatment modulates fibroblast activation, reduces profibrotic signals, reverses ECM remodeling, and supports cardiomyocyte survival.<sup>34–36</sup>

Myofibroblast modulation is particularly promising, given the central role these cells play in pathological myocardial fibrosis and impaired cardiac function. Fibrosis is driven by the activation of cardiac fibroblasts, excess ECM deposition between cardiomyocytes, in areas of



**Figure 1. Proposed mechanism of microcurrent therapy in cardiac fibrosis and remodeling.**

This figure illustrates the molecular and cellular mechanisms underlying microcurrent therapy in cardiac repair. Microcurrent therapy has been shown to modulate profibrotic and proinflammatory signaling pathways in preclinical studies, including downregulation of TGF- $\beta$ 1 (transforming growth factor  $\beta$ 1) in cultured cardiac myofibroblasts. These findings have led to the hypothesis that microcurrent therapy may promote favorable myocardial remodeling in vivo. These effects lead to decreased myofibroblast activation, suppressed fibrotic gene expression, a more physiological fibroblast phenotype, reduced extracellular matrix (ECM) accumulation, and enhanced cardiomyocyte survival. These molecular and cellular changes translate into reduced fibrosis and improved tissue remodeling, shifting the myocardium from progressive fibrotic remodeling toward structural and functional recovery.

cell death, and around blood vessels, leading to adverse remodeling and disruption of the myocardium.<sup>37</sup> These fibrotic changes are a key mechanism in most heart failure types, including HFrEF and heart failure with preserved ejection fraction, and are associated with poor treatment response and increased risk of heart failure progression and mortality.<sup>4,37</sup> Antifibrotic strategies that target cardiac fibrosis as a common end point, through pathways such as the renin-angiotensin-aldosterone system and TGF- $\beta$  signaling, inflammation, myofibroblast activation, epigenetic regulators, and fibroblast-specific surface molecules have provided important mechanistic insights and led to meaningful reductions in fibrosis. However, despite the clinical significance of these approaches, patient responses have remained modest, primarily due to redundancy among signaling pathways and systemic side effects that hinder effective, fibrosis-specific reversal.<sup>38–45</sup> In this context, microcurrent therapy

is a novel, potentially disease-modifying approach that can modulate myofibroblast activation and influence ECM remodeling.

In vitro, microcurrent exposure reduces the expression of key fibrotic and inflammatory markers, including TGF- $\beta$ 1 (transforming growth factor  $\beta$ 1) and procollagen type I, both of which are essential for pathological ECM accumulation. Additional decreases are seen in ACTA2 ( $\alpha$ -smooth muscle actin), fibronectin, and matrix remodeling enzymes, such as MMPs (matrix metalloproteinases) and their TIMPs (tissue inhibitors). These changes suggest a partial reversal of the myofibroblast phenotype toward a less-activated state. Consequently, microcurrent may influence ECM remodeling and tissue stiffness in cultured cardiac myofibroblasts. The TGF- $\beta$  pathway, a master regulator of fibrosis, is  $\text{Ca}^{2+}$ -regulated. ECM/remodeling genes, fibronectin, and MMPs are regulated by  $\text{Ca}^{2+}/\text{Na}^{+}/\text{K}^{+}$  signaling via ion channels

(TRPV4, KCa3.1, voltage-gated) and membrane potential changes, implying that microcurrent affects these pathways.<sup>46,47</sup> Transcriptomic analyses support this phenotypic shift, revealing downregulation of immune and inflammatory gene sets.<sup>34</sup> Together, these findings suggest an antifibrotic and anti-inflammatory response at the cellular level.

Single-cell and lineage-tracing studies have highlighted the heterogeneity of cardiac fibroblasts in injury and heart failure, including their distinct proinflammatory, profibrotic, and reparative substates that actively engage in immune crosstalk and ECM regulation. This has shifted emerging therapeutic approaches toward selectively modulating fibroblast activity, including targeting mechanosensitive pathways (as reviewed in<sup>48</sup>). In this context, microcurrent therapy may influence fibroblast activity and downstream ECM remodeling, offering a potential mechanistic explanation for the clinical observations in C-MIC studies.

In cardiomyocytes, the direct effect of microcurrent on contractile function remains only partially understood. Existing evidence indicates that microcurrent treatment improves cell survival, stress resistance, and proliferative ability in cardiomyocytes from both young and aged spontaneously hypertensive rats.<sup>35,36</sup> Neonatal and young cardiomyocytes have intrinsically higher proliferative capacity. Young spontaneously hypertensive rats showed a significant increase in cardiomyocyte number after microcurrent treatment, while older spontaneously hypertensive rats had a modest, nonsignificant increase. These findings suggest a protective and adaptive response rather than a primary proliferative effect in adult cardiomyocytes. Such effects may help reshape the cellular environment of the injured myocardium and contribute to improved tissue integrity and functional recovery.

Collectively, in vitro findings support a multicellular mechanism involving coordinated effects on fibroblasts, extracellular matrix remodeling, and cardiomyocyte viability, aligning with clinical observations, and indicating that microcurrent therapy modulates structural remodeling and inflammatory pathways as part of a tissue-level response that improves cardiac function.<sup>35,36</sup>

However, the proposed antifibrotic effects and modulation of TGF- $\beta$  signaling are primarily based on in vitro studies in cardiac fibroblasts and myofibroblasts, with limited validation in human cardiac tissue. Additional mechanistic studies in human cardiac cells and ongoing clinical trials are needed to establish whether the in vitro antifibrotic effects translate into meaningful clinical benefit. Furthermore, while some supportive in vivo data exist, including findings from spontaneously hypertensive rat models, they remain preliminary and require confirmation in larger, more clinically relevant models. Consequently, the translational gap between the available mechanistic evidence and the observed clinical outcomes remains an important limitation.

## Mechanistic Theories From Electrical Stimulation Biology

Clinical studies with C-MIC have generated promising preliminary findings, and in vitro studies suggest that microcurrent therapy may modulate cellular processes relevant to cardiac remodeling and function. A central unresolved question is how a microampere-scale current provokes such significant physiological changes. Insights from years of clinical studies, in vitro experiments, and foundational studies with ES on cardiac physiology provide a framework.

Cardiac bioelectric therapy, dating back to the 1960s, has evolved from arrhythmia management<sup>49,50</sup> to applications in cardiac regeneration and tissue engineering.<sup>26,51–53</sup> In vitro and engineered tissue models have shown that ES can influence cardiomyocyte differentiation,<sup>54–60</sup> cardiomyocyte maturation,<sup>61–68</sup> alignment,<sup>69</sup> gene expression,<sup>70,71</sup> cytoskeletal organization, contractility,<sup>9,72–75</sup> and functional coupling,<sup>76</sup> including in our own C-MIC studies.<sup>11</sup> Early ES application upregulates cardiac transcription factors and promotes metabolic programming, while later stages facilitate improved calcium handling and structural maturation.<sup>54,55,62,63,65</sup>

Multicellular coculture models further indicate that ES can enhance coupling and organization among cardiomyocytes, endothelial cells, and fibroblasts, supporting tissue maturation and function.<sup>66,77</sup> Similarly, human-induced pluripotent stem cell-derived cardiac spheroids exhibit improved contractility and reduced arrhythmogenicity with electrical cues.<sup>78,79</sup> The C-MIC device applies this principle throughout the myocardium, promoting synchronous, functional, and structural remodeling.

ES promotes cardiac differentiation of human-induced pluripotent stem cells, improving their suitability for myocardial infarction therapy,<sup>80</sup> and regulates reparative pathways such as connective tissue growth factor signaling.<sup>81</sup> In addition, preconditioning cardiac progenitor cells with ES boosts survival and paracrine signaling, improving function in right ventricular heart failure models.<sup>82</sup> While C-MIC does not involve cell transplantation, in vitro findings align with broader mechanistic understanding, including effects on proinflammatory and profibrotic pathways, and also enhance cardiomyocyte survival, suggesting a reparative phenotype. Whether microcurrent can activate resident progenitors in the adult human heart opens intriguing avenues for exploring its regenerative potential, especially given the observed long-term structural changes in treated patients.

Electrical cues influence cardiac electrophysiology, structure, and biochemistry, forming the basis for modern device-based approaches. Clinically, ES-based devices have reshaped the management of chronic heart failure, especially in patients with reduced ejection fraction. Fudim et al<sup>83</sup> highlight a rapid expansion in the development and clinical application of implantable devices.

Cardiac resynchronization therapy addresses electrical dyssynchrony and improves ventricular coordination<sup>84,85</sup>; cardiac contractility modulation delivers nonexcitatory signals during the refractory period to enhance contractility<sup>72,73</sup>; the Barostem aims to harness bioelectric and biologic cues to promote myocardial repair.<sup>86</sup> All 3 approaches emphasize the broader principle that electrical modulation promotes myocardial remodeling beyond electrophysiological effects. C-MIC offers advantages over cardiac resynchronization therapy, cardiac contractility modulation, and Barostem by using ultra-low, nonexcitatory microcurrents that prevent pacing artifacts and enable lasting reverse remodeling for up to 24 months (Figure 2).

Microcurrent-Specific Mechanistic Theories

Microcurrent therapy uses bioelectric cues to modulate cellular signaling, involving ions such as Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, and Ca<sup>2+</sup> that generate voltage gradients and charge transfer at the electrode interface. It is currently the only cardiac bioelectric device in clinical trials, aiming for reverse remodeling as the primary end point.<sup>31</sup>

Evidence from in vivo and in vitro studies, along with years of ES research, supports a multifactorial mechanism that exerts therapeutic effects through multiple pathways, integrating antifibrotic, anti-inflammatory, and proregenerative effects.

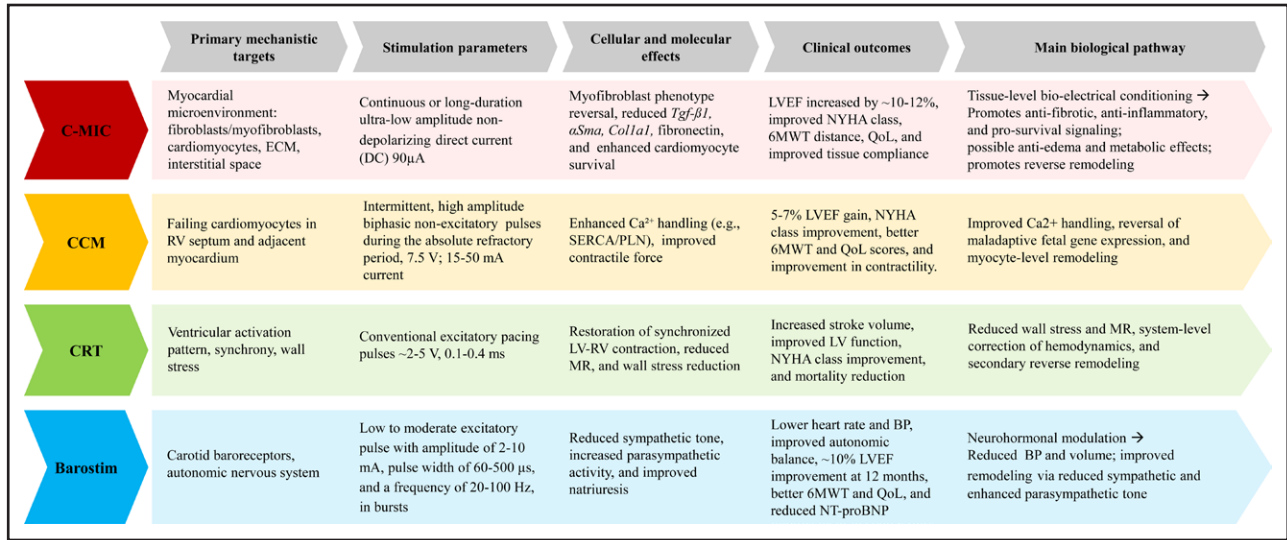
- Evidence-based mechanisms:
- Antifibrotic: Attenuates myofibroblast activation, ECM deposition, fibrosis, and wall stiffness, aligning with gradual reverse remodeling seen by echocardiography.<sup>31,34</sup>

- Anti-inflammatory: Suppresses profibrotic and inflammatory signaling, enhances functional status (NYHA class, quality of life), and reduces myocardial stress.<sup>31,34</sup>
  - Cytoprotective: Preserves cardiomyocyte viability and survival, contributing to long-term improvement of LVEF.<sup>31,35,36</sup>  
Speculative mechanisms:
    - Electro-osmosis may reduce myocardial edema through microcurrent-induced fluid shifts, improving tissue compliance and cardiac output, as suggested by preclinical observations.<sup>33</sup>
    - Ion channel modulation: Bioelectrical cues can alter membrane potential, redox balance, metabolism, and mitochondrial function, subtly influencing cellular responses to injury.
    - Regeneration: May involve activating resident progenitor cells or paracrine signaling, leading to ongoing structural remodeling and continuous improvements.
- The proposed antifibrotic mechanism is supported by early preclinical and in vitro studies with limited in vivo validation and remains to be confirmed in translational settings.

 American Heart Association

FUTURE DIRECTIONS FOR MECHANISMS, TRANSLATION, AND CLINICAL EXPANSION

Future studies will take a mechanistic and translational approach to define how microcurrent influences cardiac tissue beyond direct cellular effects. One unexplored mechanism is the modulation of intercellular signaling networks, including paracrine and bioelectrical coupling. Another potential mechanism is the extracellular ionic and redox environment. Ongoing research using specialized electrode setups aims to distinguish electric-field

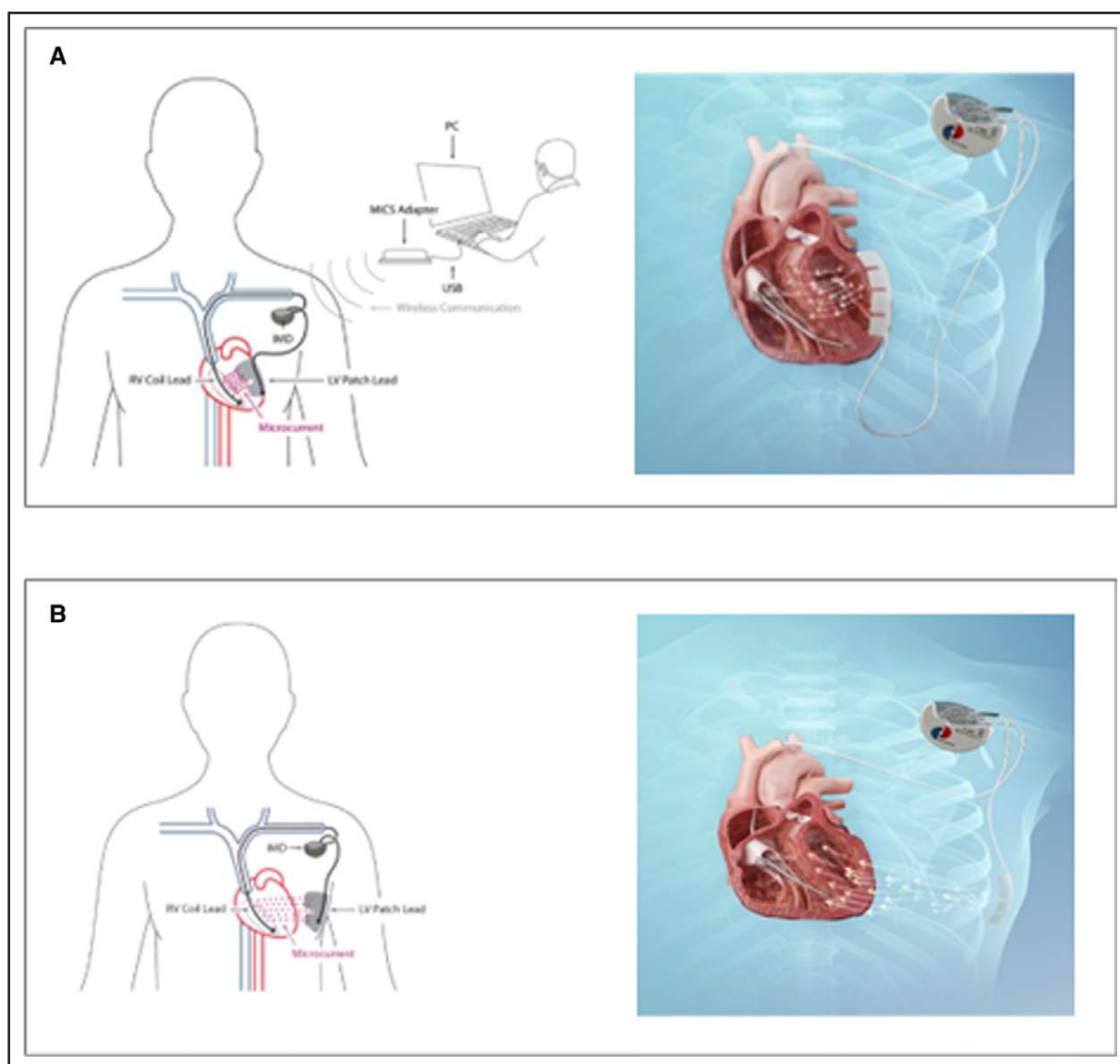


**Figure 2. Mechanistic comparison of cardiac device-based therapies.** The schematic summarizes and compares 4 device-based therapies for heart failure with reduced ejection fraction (HFrEF): cardiac microcurrent (C-MIC), cardiac contractility modulation (CCM), cardiac resynchronization therapy (CRT), and baroreflex activation therapy (Barostim). Each therapy is mapped according to its primary biological targets, downstream cellular and molecular effects, and key clinical outcomes, linking the mechanism of action to functional improvements, cardiac remodeling, and enhanced cardiac performance.

effects from byproducts by monitoring pH shifts, ion variations, and redox changes. These changes may impact pathways involved in calcium handling and ROS-mediated signaling.<sup>53,87</sup>

In terms of the translational roadmap, current in vitro models of fibrosis and hypoxia will be extended to primary human cardiac cells and clinically relevant animal models. In parallel, molecular profiling approaches, including multiomics and targeted gene expression analyses, will be important for identifying biomarkers of microcurrent response, clarifying the underlying mechanisms of action, and establishing links between mechanistic findings and clinical outcomes.

Given the shared roles of fibrosis, inflammation, and maladaptive remodeling across cardiovascular diseases, the potential effects of microcurrent therapy could be evaluated in a broad range of conditions, including heart failure with preserved ejection fraction, postmyocardial infarction remodeling, diabetic cardiomyopathy, hypertensive heart disease, valvular heart disease associated with left ventricular remodeling, and fibrotic cardiomyopathies. For example, myocardial fibrosis and increased ventricular stiffness are central pathophysiological features of heart failure with preserved ejection fraction, while postmyocardial infarction remodeling is characterized by inflammation, scar formation, and progressive ventricular



**Figure 3. Configurations of the cardiac microcurrent (C-MIC) delivery system.**

**A**, Surgical configuration: the original C-MIC setup showing an epicardial left ventricular (LV) patch electrode implanted via a left mini-thoracotomy and positioned directly on the LV epicardial surface to deliver continuous microcurrent across the myocardium. **B**, Subcutaneous configuration: a less invasive configuration in which the LV patch electrode is positioned subcutaneously on the chest wall rather than directly on the epicardium. This setup is combined with an intracardiac lead to allow microcurrent delivery across the myocardium while avoiding surgical thoracotomy and epicardial access.

remodeling that contribute to long-term cardiac dysfunction. In these conditions, the potential effects of microcurrent therapy on fibroblast activity, extracellular matrix remodeling, and tissue repair warrant further investigation. At present, however, the potential role of microcurrent therapy beyond nonischemic HFrEF remains speculative. Dedicated mechanistic studies, disease-specific preclinical models, and appropriately designed clinical trials will be required to determine whether the biological effects observed to date translate into meaningful clinical benefits across these diverse disease states.

A subcutaneous microcurrent delivery approach has been developed to improve the translational potential of C-MIC therapy by reducing invasiveness while maintaining its biological effects. It uses a subcutaneous electrode and an intracardiac lead to deliver ultra-low-amplitude direct current across the myocardium, performed in the catheterization laboratory under conscious sedation without thoracotomy or surgical epicardial access (Figure 3A and 3B), using techniques familiar to interventional cardiologists and electrophysiologists experienced in implanting pacemakers, implantable cardioverter-defibrillators, and other implantable cardiac electronic devices. This approach may improve safety, simplify implementation, and broaden application to patients, including those unsuitable for surgery or advanced therapies, such as patients with mild-reduction LVEF from ischemic and nonischemic etiologies and patients with early-stage heart failure. The subcutaneous system is currently being evaluated in the ongoing C-MIC III study (REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT06920030) for feasibility and safety. Building on these data, a double-blind, sham-controlled trial (C-MIC IV) is planned as the critical next step to rigorously evaluate the safety and efficacy of subcutaneous microcurrent therapy, while controlling for placebo effects and other potential sources of bias. The subcutaneous microcurrent platform represents an important advancement by combining the mechanistic rationale of microcurrent therapy with a less invasive, more scalable implantation approach. If proven safe and effective, this platform could facilitate broader adoption and expand access to microcurrent therapy.

## CONCLUSIONS

Microcurrent therapy is a promising approach to cardiac repair through modulation of endogenous bioelectric signals. Preclinical studies suggest potential effects on fibrosis, inflammation, and cardiomyocyte survival in vitro, supporting a multifactorial mechanism of action. However, the underlying signaling pathways remain incompletely understood, and their relevance to human tissue has yet to be established. Continued investigation in physiologically relevant preclinical models, together with rigorous controlled clinical studies, will be essential

to further define the mechanisms of action, validate the biological effects observed to date, and determine the therapeutic potential of microcurrent therapy in heart failure and other cardiovascular diseases.

## ARTICLE INFORMATION

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### Author Contributions

All authors contributed to the conception and design of the article. The initial draft was prepared with significant intellectual and editorial input from Drs Rame, Bachamanda Somesh, and Kallel. All coauthors, including Drs Lanfear, Fudim, Drakos, Burkhoff, MacLeod, Butler, González Miqueo, and Anker, reviewed, edited, and approved the final manuscript.

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Drs Bachamanda Somesh and Kallel are employees of Berlin Heals. All other authors, including Drs Rame, Lanfear, Fudim, Drakos, MacLeod, Butler, and Anker, are consultants, except Drs González Miqueo and Burkhoff. The other authors report no conflicts.

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