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Indian Journal of Clinical Anatomy and Physiology

Journal homepage: https://www.ijcap.org/

Review Article

Cardiac remodelling and regeneration: State of the science, translational pathways, and clinical outlook

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Abstract

Cardiac remodelling—structural, cellular, and molecular changes that reshape the heart after stress or injury—drives heart failure progression. In contrast, cardiac regeneration refers to the replacement of lost myocardium with new, functional tissue. Adult human hearts exhibit very low baseline cardiomyocyte renewal (<1% per year), insufficient to recover from large injuries, so post-infarction "healing" usually culminates in non-contractile scar and adverse remodelling. Recent advances across single-cell/spatial omics, comparative biology (zebrafish, neonatal mouse), mechanobiology (Hippo–YAP), immunology, biomaterials, engineered tissues, gene/mRNA delivery, and extracellular vesicles (EVs) are reshaping the translational landscape. Meanwhile, guideline-directed medical therapies (e.g., ARNI, SGLT2 inhibitors) and devices can induce reverse remodelling, improving volumes and function but without true remuscularization. This review synthesizes mechanistic insights and late-breaking evidence, outlines therapeutic strategies moving from paracrine repair to bona fide remuscularization, and highlights key hurdles for durable, arrhythmia-safe regeneration in humans.

Keywords: Cardiac remodelling, Cardiac regeneration, Reverse remodelling, Cardiomyocyte proliferation, Fibrosis, Hippo–YAP signalling, Stem cell therapy, Extracellular vesicles

Received: 17-07-2025; **Accepted:** 22-08-2025; **Available Online**: 15-09-2025

1. Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide, accounting for nearly 18 million deaths annually, with ischemic heart disease and heart failure representing the greatest contributors.[1] Among the pathophysiological processes that underlie progression from cardiac injury to heart failure, cardiac remodelling occupies a central role. Remodelling encompasses structural, cellular, and molecular alterations that occur in response to stressors such as myocardial infarction (MI), hypertension, volume overload, valvular disease, and cardiomyopathy.[2] These changes include myocyte loss, hypertrophy of surviving cells, fibroblast activation with interstitial and replacement fibrosis, extracellular matrix (ECM) remodelling, and maladaptive alterations in chamber geometry and mechanics.[2,3] While initially compensatory, remodelling ultimately promotes ventricular dilation, systolic and diastolic dysfunction, arrhythmogenesis, and progression to overt heart failure. Despite improvements in pharmacological and device-based therapies, the global burden of heart failure is rising, with an estimated 64 million patients affected worldwide, particularly in aging populations.[1] A major reason for poor outcomes is that current therapies, although capable of reducing neurohormonal stress and inducing reverse remodelling (i.e., partial restoration of ventricular size, shape, and function), do not replace lost cardiomyocytes.[4] After MI, for example, nearly one billion cardiomyocytes can be lost, and the adult human heart displays minimal intrinsic regenerative capacity—approximately 0.5–1% annual cardiomyocyte turnover, declining further with age.[5] Thus, injured myocardium typically heals through scar formation, preserving structural integrity but severely compromising contractile function.

In contrast, cardiac regeneration refers to the restoration of myocardium through the generation of new, functional cardiomyocytes, vascular elements, and supportive stromal tissue.[6] While certain organisms such as zebrafish and neonatal mammals (e.g., mice in the first week of life) exhibit

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http://doi.org/10.18231/j.ijcap.v.12.i.3.5

robust regenerative potential,[7,8] this capacity is almost entirely lost in adult mammals, including humans. Understanding the biological basis of regeneration and applying these insights to therapeutic strategies has become a major frontier in cardiovascular research. The last decade has witnessed transformative advances in technologies that dissect and modulate remodelling and regeneration, including single-cell and spatial multi-omics, mechanobiology of Hippo–YAP signalling, immune-modulatory pathways, stem cell and engineered tissue therapies, extracellular vesicle biology, and targeted gene/mRNA delivery platforms[9-12] Furthermore, contemporary clinical therapies such as angiotensin receptor–neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated impressive ability to promote reverse remodelling, highlighting the possibility of pharmacological modulation of structural cardiac adaptation.[13,14] Yet, these represent functional repair rather than true remuscularization.

The central challenge in cardiovascular medicine, therefore, is to bridge the gap between remodelling and regeneration: to not only halt or reverse maladaptive remodelling, but also to repopulate scarred myocardium with new, electromechanically integrated cardiomyocytes. This requires coordinated control of multiple biological processes—cell proliferation, fibroblast reprogramming, ECM remodelling, angiogenesis, and immunomodulation—within a permissive cardiac niche. The present review synthesizes the current state of knowledge in cardiac remodelling and regeneration, with emphasis on recent mechanistic insights, translational strategies, and clinical advances. We explore: (i) the molecular and cellular basis of remodelling; (ii) lessons from comparative biology in regenerative species; (iii) emerging human cell-state atlases in health and disease; (iv) pharmacological and device-based modulation of remodelling; and (v) cutting-edge approaches in bioengineering, gene therapy, and regenerative medicine. We also discuss safety considerations, trial design, and future perspectives. By integrating these dimensions, this article highlights the opportunities and barriers on the path to true myocardial regeneration in humans, and outlines how new discoveries may transform clinical outcomes in heart failure and ischemic cardiomyopathy.

2. Cellular and Molecular Bases of Remodelling

1. **Cardiomyocytes:** cell-cycle arrest, ploidy, and mechano-signalling: Postnatal mammals rapidly exit the cell cycle; polyploidization and sarcomere maturation constrain proliferation. Mechano-transduction via Hippo–YAP/TAZ links cell–cell junctions and cytoskeleton to gene programs that can re-open proliferation when activated in models, albeit with oncogenic/arrhythmic risk if dysregulated.[10]
2. **Fibroblasts and extracellular matrix (ECM):** After injury, resident fibroblasts differentiate into myofibroblasts, depositing collagen that preserves structure but stiffens the ventricle and impedes electromechanical coupling. Emerging work maps fibroblast states and ECM niches that might be modulated to limit scar and permit myocyte repopulation.[2].
3. **Vascular and immune components:** Neovascularization and immune orchestration—especially macrophage phenotypes—govern whether healing tends toward scar or regeneration. Macrophages can be pro-regenerative in neonatal mice and pro-fibrotic in adults; tuning their states is a therapeutic lever.[15]
4. **Human cardiac cell-state atlases in remodelling:** High-resolution single-cell and spatial transcriptomic maps now catalogue human cardiomyocytes, fibroblasts, endothelial and immune subsets across healthy and failing hearts.[9,16] These atlases reveal disease-specific myofibroblast programs, endothelial-to-mesenchymal transitions, and inflammatory niches at the scar border, generating druggable hypotheses and biomarkers for patient stratification.
5. **Modulating remodelling with current therapies (Reverse Remodelling):** While not regenerative, modern therapies favourably reshape the ventricle:

ARNI (sacubitril/valsartan) improves LV volumes, mass, and ejection fraction vs. ACEi/ARB in HFrEF in multiple cohorts/meta-analyses.[17-18]

SGLT2 inhibitors (dapagliflozin/empagliflozin) consistently promote reverse remodelling on echo/CMR and reduce filling pressures across HF phenotypes.[14,19]

These effects likely reflect hemodynamic unloading, natriuretic and metabolic reprogramming, antifibrotic/anti-inflammatory actions, and improved microvascular function—functional repair without new muscle.[2]

3. Toward Regeneration: Therapeutic Strategies

1. **Re-activating cardiomyocyte proliferation:** Hippo–YAP pathway activation in adult mammalian hearts induces myocyte cell-cycle entry and partial regeneration in models; safe, targeted, and transient control remains the key translational challenge.[10] ERBB2/Neuregulin-1 signalling can trigger adult cardiomyocyte dedifferentiation and proliferation in mice, offering another orthogonal axis.20 [20].
2. **Immuno-regeneration:** Fine-tuning macrophage subsets (e.g., CCR2− reparative vs. CCR2+ inflammatory) and timing of inflammation resolution

is central to productive healing, as shown in neonatal models and human disease atlases.[15]

3. **Gene, mRNA, and epigenetic interventions:** Vectorized delivery (AAV, LNP-mRNA) of pro-regenerative factors or cycle regulators is under active preclinical study, with emphasis on transient expression to minimize arrhythmia and oncogenesis; partial reprogramming and base-editing are emerging but not yet ready for clinical myocardium-wide use.[2]

4. **Extracellular vesicles and secretomes:** EVs derived from pluripotent or cardiac cells improve function, angiogenesis, and fibrosis in large-animal and rodent MI models—capturing the paracrine benefits of cell therapy without engraftment.[11]

5. **Engineered tissues and cells:** Pluripotent stem cell–derived cardiomyocytes (PSC-CMs) delivered as patches/sheets or thick engineered tissues can re-muscularize injured myocardium in large animals, but electrical integration and ventricular arrhythmias remain critical risks observed in nonhuman primates.[21] First-in-human iPSC-CM patches/sheets for ischemic cardiomyopathy have entered safety-focused trials in Japan, with initial case reports indicating feasibility; efficacy and long-term arrhythmia surveillance are pending.[22,23]

Comparative Regeneration - Lessons from Nature: One of the most intriguing avenues in regenerative cardiology comes from studying organisms that possess an extraordinary ability to regenerate their hearts. Unlike the adult human heart, which shows limited regenerative capacity, certain species such as zebrafish, axolotls, and neonatal mammals exhibit robust cardiac regeneration following injury. Understanding these mechanisms provides critical insights into how regeneration might be reactivated in the human heart.

1. **Zebrafish (*Danio rerio*):** Zebrafish have become the quintessential model of cardiac regeneration. Following apical resection, cryoinjury, or genetic ablation of cardiomyocytes, zebrafish hearts can regenerate up to 20% of their ventricular tissue within weeks, restoring both structure and function.[24,25] This regenerative process relies on proliferation of pre-existing cardiomyocytes, rather than stem cell recruitment, with cardiomyocytes re-entering the cell cycle and replacing lost tissue. Key signalling pathways involved include Fibroblast Growth Factor (FGF), Notch, Retinoic Acid, and Hippo–YAP signalling.[26] Additionally, zebrafish display limited fibrosis during repair, with transient extracellular matrix deposition that resolves as functional myocardium is restored.[27] This contrasts with human healing, where excessive fibrosis leads to scar formation and adverse remodelling.

2. **Axolotls (*Ambystoma mexicanum*):** Axolotls, a species of salamander, also demonstrate extraordinary regenerative capacity, not only for limbs but also for cardiac tissue. After ventricular resection, axolotls can regenerate myocardium without fibrotic scar formation.[28] Regeneration is driven by dedifferentiation of cardiomyocytes, increased cell cycle re-entry, and integration with vascular and extracellular matrix remodelling.[29] Unlike mammals, axolotls maintain a more "permissive" extracellular environment, which appears essential for tissue plasticity. These features highlight the importance of ECM remodelling and immune regulation in determining whether regeneration or fibrosis predominates.

3. **Neonatal Mammals:** Interestingly, mammals also retain regenerative potential — but only for a short developmental window. In neonatal mice, cardiac injury during the first seven days of life can result in complete regeneration of the heart.[8] During this period, cardiomyocytes are still capable of proliferating, resembling the regenerative response seen in zebrafish. However, this ability is rapidly lost as cardiomyocytes exit the cell cycle, undergo polyploidization, and the extracellular environment becomes more fibrotic.[30] Studies in neonatal pigs and even limited evidence in human infants suggest that this regenerative window may be conserved across mammalian species.[31] Understanding why this regenerative potential is lost with maturation is a central question in translational cardiology.

Lessons for Human Therapy: These natural models highlight several principles that could inform therapeutic strategies in humans:

1. **Cardiomyocyte Plasticity** – The ability of cardiomyocytes to re-enter the cell cycle is central to regeneration. Stimulating similar responses in human cardiomyocytes, potentially via Hippo–YAP or Neuregulin–ERBB2 signalling, could restore proliferative capacity.[20]

2. **Controlled Fibrosis** – Regenerative species minimize scar formation by balancing temporary ECM deposition with timely remodelling. Therapeutics that shift the balance from fibrosis to regeneration could enhance recovery after myocardial infarction.

3. **Immune Modulation** – Macrophages in zebrafish and axolotls promote regeneration rather than chronic inflammation. Harnessing regenerative immune signaling in humans may improve outcomes.[32]

4. **Developmental Timing** – The neonatal mammalian window suggests that regeneration is not entirely foreign to mammals but suppressed with age.

Identifying and reversing the molecular switches that terminate this regenerative capacity could reopen regenerative potential in adults.

In summary, comparative regeneration studies provide a blueprint for reawakening dormant pathways in the human heart. The challenge lies in translating these evolutionary insights into safe, effective, and clinically applicable therapies for heart failure patients.

4. Discussion

Cardiac remodelling and regeneration represent two opposing yet interconnected processes that ultimately determine clinical outcomes in patients with heart disease. Remodelling reflects a maladaptive response to myocardial injury or chronic stress, leading to fibrosis, chamber dilation, contractile dysfunction, and arrhythmias, while regeneration embodies the therapeutic promise of restoring functional myocardium through cellular replacement and tissue integration.[2,3] Bridging these two processes is the central challenge for contemporary cardiovascular medicine.

4.1. Clinical relevance of remodelling

Clinical evidence has consistently demonstrated that the extent of adverse remodelling strongly correlates with morbidity and mortality in heart failure.[4] Imaging markers such as left ventricular end-diastolic volume (LVEDV), sphericity index, and ejection fraction (EF) serve as powerful predictors of outcomes.[33] Pharmacological interventions such as ARNIs and SGLT2 inhibitors are now recognized not only for their hemodynamic and metabolic effects but also for their capacity to induce reverse remodelling, evidenced by reduced chamber size and improved EF.[13,14] However, these therapies remain palliative rather than curative, as they do not address the fundamental deficit in cardiomyocyte number.

4.2. Barriers to regeneration

The adult human heart exhibits only minimal regenerative capacity, with cardiomyocyte turnover rates of <1% per year, insufficient to compensate for large-scale loss after myocardial infarction.[5] Several barriers account for this limitation:

1. Cell-cycle arrest in adult cardiomyocytes, driven by epigenetic silencing and checkpoint regulation.[34]
2. Fibrotic scar formation, which stabilizes ventricular wall stress but creates a non-conductive and non-contractile substrate.[35]
3. Inflammatory and immune responses that resolve tissue damage but often inhibit regenerative pathways.[36]

Comparative biology studies in zebrafish and neonatal mammals demonstrate that regeneration requires a permissive environment in which cardiomyocytes can dedifferentiate, proliferate, and re-integrate with minimal fibrosis.[7,8] Translating these principles into adult human therapy remains an ongoing pursuit.

4.3. Emerging regenerative strategies

Multiple strategies are under exploration to induce or enhance regeneration:

1. **Stem cell and iPSC-derived cardiomyocyte transplantation:** Preclinical studies have demonstrated partial improvements in contractility, but challenges include poor engraftment, arrhythmogenic risk, and immune rejection.[37,38]
2. **Engineered heart tissue (EHT):** Advances in biomaterials and bio-fabrication allow for the generation of vascularized, electrically conductive cardiac patches that integrate with host myocardium.[12] Early-phase clinical trials are underway in Europe and Asia.[39]
3. **Gene and RNA therapies:** Targeting the Hippo–YAP, ERBB2, and cell-cycle regulators has shown promise in reactivating cardiomyocyte proliferation.[10] mRNA-based therapies, inspired by COVID-19 vaccine platforms, are being tested for safe transient delivery of regenerative factors.[40]
4. **Extracellular vesicles (EVs) and secretome therapies:** EVs derived from stem cells or cardiomyocytes contain microRNAs and proteins that reduce fibrosis, modulate immunity, and promote angiogenesis.[11]
5. **Direct cardiac reprogramming:** Conversion of resident fibroblasts into induced cardiomyocyte-like cells via transcription factor cocktails is a promising avenue, though efficiency and safety remain limiting factors.[40]

4.4. Translational challenges and future directions

Despite major progress, several translational hurdles persist:

1. **Arrhythmia risk:** Integration of newly formed cardiomyocytes with host myocardium must achieve synchronous electrical coupling to prevent ventricular tachyarrhythmias.[42]
2. **Immune compatibility:** Both cell-based and gene-based therapies may trigger immune responses; development of hypoimmunogenic iPSCs and immune-tolerant biomaterials is crucial.[43]
3. **Delivery methods:** Efficient and safe delivery remains a major challenge. Intramyocardial injection, epicardial patches, and systemic administration of nanoparticles each have advantages and limitations.[44]

4. **Long-term durability:** Sustained benefit requires that regenerated tissue not only survives but also adapts to long-term hemodynamic stresses.

Looking forward, multi-modal therapies that combine anti-remodelling agents (ARNIs, SGLT2i, β-blockers) with regenerative platforms (engineered tissue, gene therapy, EVs) may provide the most effective clinical outcomes.[6] Integration of AI-based imaging and multi-omics profiling will likely improve patient selection, monitoring, and personalization of regenerative therapies.[9] In conclusion, while remodelling remains a central pathological process in heart disease, ongoing advances in regenerative medicine offer the possibility of true myocardial restoration. Success will depend on synergizing anti-remodelling pharmacology with regenerative biology, ultimately shifting treatment from symptom management to curative myocardial repair.

4.5. Prospects

The field of cardiac remodelling and regeneration is rapidly evolving, moving from pathophysiological understanding to translational applications. While current clinical management primarily focuses on attenuating adverse remodelling, the ultimate therapeutic objective is true myocardial regeneration, restoring lost contractile mass and reversing structural dysfunction. Several prospective directions are emerging across pharmacology, bioengineering, genetics, and digital health that may redefine cardiovascular medicine in the next decade.

4.6. Integration of regenerative and anti-remodelling therapies

The next generation of heart failure therapy is likely to combine anti-remodelling pharmacology with biological regeneration. While drugs such as ARNIs, β-blockers, and SGLT2 inhibitors have demonstrated significant capacity to induce reverse remodelling,[13,14] they cannot replace lost cardiomyocytes. Coupling these with cellular or gene-based interventions may achieve synergistic outcomes — stabilizing myocardial architecture while regenerating functional myocardium.[6] Such combinatorial approaches are expected to progress to large-scale clinical trials within the next 5–10 years.

4.6. Next-generation regenerative technologies

Emerging regenerative technologies offer promising prospects:

1. **Gene-editing and epigenetic modulation:** CRISPR-based strategies are being explored to reprogram fibroblasts, modify cardiomyocyte cell-cycle arrest, and enhance tissue repair.[45]

2. **mRNA-based therapeutics:** Inspired by the success of mRNA vaccines, transient mRNA delivery of regenerative factors (e.g., VEGF, FSTL1, YAP activators) provides a safer and more controllable alternative to DNA vectors.[40]

3. **Bioprinting and engineered tissues:** Three-dimensional (3D) bioprinting of vascularized cardiac tissue is emerging as a frontier for patient-specific myocardial patches.[46] The integration of microfluidics and organ-on-chip platforms will allow personalized preclinical testing of regenerative therapies.[47]

4. **Organoid models:** Human cardiac organoids derived from iPSCs are being developed as disease models and screening tools to accelerate drug and biomaterial discovery.[48]

4.7. Immunomodulation as a therapeutic target

One of the main barriers to regeneration is the immune and inflammatory response following myocardial injury. Prospective therapies will likely focus on:

1. Immune-tolerant biomaterials that reduce foreign-body reactions.
2. Macrophage reprogramming toward pro-regenerative phenotypes (M2-like).
3. T-cell modulation to prevent autoimmunity without impairing repair.[36]
4. Harnessing the immune system not only to limit fibrosis but also to actively promote regeneration represents a critical direction in the next decade.

4.8. Digital cardiology and AI integration

Another major prospect lies in the integration of digital technologies:

1. AI-guided imaging can detect subtle patterns of remodelling earlier than conventional echocardiography or MRI, enabling precision therapy initiation.[9]

2. Wearable sensors and remote monitoring will provide continuous assessment of cardiac function, allowing early intervention in remodelling progression.[49]

3. Multi-omics integration (genomics, proteomics, metabolomics, epigenomics) will personalize regenerative therapies based on patient-specific molecular signatures.[50] Thus, digital cardiology coupled with regenerative biology may deliver highly individualized treatment pathways.

4.9. Ethical, economic, and translational considerations

As regenerative cardiology transitions from experimental models to clinical application, several prospective challenges must be addressed:

1. Safety and durability: Ensuring long-term survival and integration of regenerated tissue without tumorigenesis or arrhythmias.[42]

2. Scalability and cost-effectiveness: Regenerative therapies, especially engineered tissues and gene therapies, are resource-intensive. Ensuring global accessibility will be a critical challenge.[37]

3. Ethical oversight: Stem cell sourcing, genome editing, and use of synthetic biology tools require strict regulatory frameworks[51]

5. Safety, Efficacy, and Trial Design Considerations

The translation of regenerative and remodelling-based therapies from laboratory discoveries into clinical practice is fraught with challenges, particularly regarding safety, efficacy, and the design of clinical trials. While preclinical models have provided valuable proof-of-concept, moving into human application necessitates addressing potential risks, optimizing endpoints, and establishing standardized methodologies for evaluation.

5.1. Safety considerations

Safety is paramount in any cardiac intervention, especially in regenerative cardiology where therapies may involve cell transplantation, gene editing, or modulation of developmental pathways. Major safety concerns highlighted in Table 1. include:

1. **Arrhythmogenicity** – The introduction of immature or ectopic cardiomyocytes, especially stem cell–derived cells, poses the risk of electrical instability, leading to ventricular arrhythmias. Reports from early cell therapy trials highlighted transient arrhythmic events, emphasizing the need for electrophysiological monitoring.[52,53]

2. **Tumorigenicity** – Pluripotent stem cells, including iPSCs, carry the risk of teratoma formation if undifferentiated cells are inadvertently transplanted. Ensuring lineage commitment and genomic stability before transplantation is crucial.[54]

3. **Immune Rejection and Inflammation** – Even autologous cell sources can trigger immune responses due to culture-induced modifications. Allogeneic stem cell therapies may require immunosuppressive strategies, complicating long-term safety.[55]

4. **Off-Target Effects in Gene Therapy** – Viral vector–based therapies (e.g., AAV-mediated delivery) raise concerns of off-target integration, insertional mutagenesis, and long-term persistence. Non-integrating systems and improved vector engineering are being developed to minimize these risks.[56]

5. **Fibrotic Remodelling and Maladaptive Healing** – Excessive stimulation of proliferation or regeneration could paradoxically lead to uncontrolled tissue remodelling or fibroblast activation, impairing function rather than restoring it.[57]

6. Efficacy Considerations

Demonstrating clinical efficacy remains a major hurdle. While many preclinical studies show robust improvements in animal models, translation into humans has been modest. Key factors influencing efficacy include:

1. **Engraftment and Retention –** Cell survival after transplantation is notoriously low (<10% at one week in many trials). Strategies such as tissue engineering scaffolds, injectable hydrogels, and preconditioning aim to enhance cell retention and integration.[21]

2. **Paracrine Effects vs. True Regeneration –** Many benefits of cell therapy appear to be mediated by paracrine signalling (e.g., exosome release, growth factor secretion) rather than direct myocardial replacement. Harnessing these paracrine factors via extracellular vesicles or engineered secretomes may improve reproducibility.[58]

3. **Functional Recovery Metrics –** Improvements in left ventricular ejection fraction (LVEF) have often been modest (<5% absolute increase) in human trials. Other efficacy endpoints such as scar size reduction, functional capacity (6-minute walk test), and biomarker improvement (BNP, troponin) are being explored.[59]

4. **Patient Selection** – Heterogeneity in patient populations (acute vs. chronic ischemic cardiomyopathy, HFpEF vs. HFrEF) complicates trial outcomes. Patients with less advanced disease may respond better to regenerative interventions.[60]

7. Trial Design Considerations

The complexity of regenerative therapies requires innovative clinical trial designs beyond traditional pharmacological models. Important elements include:

1. **Randomization and Blinding** – Many early trials lacked adequate blinding, leading to placebo-driven functional improvements. Future studies must incorporate sham controls or double-blind designs to establish true efficacy.[61]

2. **Endpoints Beyond Mortality** – While mortality remains a gold standard endpoint in cardiology, regenerative trials may need composite endpoints that capture structural, functional, and quality-of-life improvements. Imaging-based endpoints (MRI scar quantification, strain analysis) are gaining importance.[62]

3. **Long-Term Follow-Up** – Unlike drugs, regenerative interventions may have delayed or cumulative effects. Monitoring for late arrhythmias, tumorigenesis, or fibrosis requires follow-up beyond 2–5 years.[63]

4. **Adaptive Trial Designs** – Given the novelty of these therapies, adaptive designs that allow modifications in dosing, patient stratification, and biomarker inclusion can improve trial efficiency while ensuring safety.[64]
5. **Regulatory and Ethical Oversight –** Regulatory agencies such as the FDA and EMA emphasize Good Manufacturing Practice (GMP) compliance, batch consistency, and rigorous safety reporting for cell and gene therapies. Ethical considerations, particularly for gene-editing approaches like CRISPR, require robust informed consent and long-term monitoring.[65]

8. Balancing Innovation with Patient Safety

Ultimately, the promise of cardiac regeneration must be balanced with cautious optimism. A pragmatic approach emphasizes gradual translation, beginning with small, carefully monitored Phase I/II trials, optimizing safety, and progressively expanding into larger Phase III efficacy trials. Integration of multidisciplinary expertise—including cardiologists, bioengineers, geneticists, and ethicists—will be crucial to designing trials that are scientifically rigorous and ethically sound.

Table 1: Major safety concerns in regenerative cardiology

Challenge	Description / Concern	Proposed Solutions / Mitigation Strategies
Arrhythmogenicity	Immature cardiomyocytes or ectopic cell integration can trigger ventricular arrhythmias	Careful electrophysiological screening; genetic modification to enhance conduction coupling (e.g., connexin-43 overexpression); long-term ECG monitoring
Tumorigenicity	Risk of teratoma formation from residual pluripotent stem cells	Pre-transplant differentiation protocols; purification methods (FACS sorting, suicide genes); genomic stability testing
Immune Rejection	Allogeneic cells or modified autologous cells can trigger host immune response	Use of immunosuppressants; gene editing to reduce HLA expression (“universal donor” cells); encapsulation technologies
Off-target Gene Therapy Effects	Viral vectors may integrate into unintended sites, causing mutagenesis	Use of non-integrating vectors (AAV, adenovirus); CRISPR base editors with higher specificity; improved vector engineering
Poor Cell Engraftment and Retention	<10% of transplanted cells survive long term in myocardium	Tissue engineering scaffolds, injectable hydrogels, preconditioning with pro-survival factors, ischemic preconditioning
Fibrotic Remodelling	Excessive or maladaptive fibrosis may impair contractility	Combination therapy with anti-fibrotic drugs; modulation of TGF-β pathway; precision dosing of regenerative signals
Limited Functional Recovery	Modest improvements in LVEF and clinical outcomes	Focus on paracrine therapies (exosomes, secretomes); use of cardiac patches; repeated dosing strategies
Patient Heterogeneity	Responses differ in acute vs. chronic heart failure or ischemic vs. non-ischemic cases	Careful patient selection; stratified trial design; biomarker-driven inclusion criteria
Unclear Clinical Endpoints	Mortality alone may not capture regenerative benefit	Use of composite endpoints (scar size reduction, exercise capacity, BNP levels, MRI functional imaging)
Long-Term Safety Uncertainty	Potential late arrhythmias, fibrosis, or tumorigenesis after therapy	Extended follow-up (≥5 years); patient registries; adaptive monitoring protocols

9. Outlook

The field of cardiac remodelling and regeneration is advancing at an unprecedented pace, bridging the gap between basic discoveries and translational applications. Yet, despite the rapid expansion of knowledge, significant challenges remain before regenerative strategies can become a mainstream therapeutic option for heart failure patients. The outlook for this field is shaped by a combination of scientific, clinical, and technological factors that will define the trajectory of progress over the next decade. The outlook for cardiac remodelling and regeneration is defined by the interplay of scientific innovation, technological advancement, clinical trial design, and ethical oversight. Progress in this field has the potential not only to revolutionize heart failure management but also to provide a blueprint for regenerative strategies across other organ systems. With continued interdisciplinary collaboration and careful regulatory navigation, the vision of a regenerating human heart is gradually moving from aspiration to reality.

1. **Bridging Basic Science and Clinical Application:** While preclinical studies in small and large animal

models have demonstrated promising regenerative outcomes, translation to human patients remains limited. Differences in myocardial structure, immune responses, and regenerative capacity pose significant barriers. Future efforts must emphasize rigorous comparative studies, scalable preclinical models, and clinically relevant endpoints to ensure the bench-to-bedside pipeline is robust and reliable.[66]

2. **Personalized and Precision Regeneration:** The future of cardiac regeneration will likely be patient-specific. Variability in genetic predisposition, comorbidities, and environmental influences strongly affects therapeutic responses. Personalized medicine approaches, including patient-derived induced pluripotent stem cells (iPSCs), biomarker-guided therapies, and precision gene editing, hold promise in tailoring regenerative therapies to individual patients.[67] The incorporation of artificial intelligence (AI) and machine learning in analysing large-scale clinical and molecular datasets could enable prediction of therapy responders versus non-responders.

3. **Integrative and Combination Therapies:** It is increasingly evident that a single intervention—be it cell therapy, gene editing, or biomaterial support—may not suffice for complete cardiac regeneration. The outlook points toward multimodal approaches, combining cardiomyocyte induction with anti-fibrotic therapy, immune modulation, angiogenesis promotion, and bioengineered scaffolds.[68] Such combinatorial strategies may synergistically enhance myocardial repair and improve outcomes compared to monotherapies.

4. **Next-Generation Biomaterials and Delivery Platforms:** Emerging biomaterials, including smart hydrogels, injectable scaffolds, and extracellular vesicle (EV)-loaded nanoparticles, are expected to play a central role in controlled and targeted delivery of regenerative agents. These materials not only enhance cell retention and survival but also provide mechanical support to the damaged myocardium, thereby improving functional recovery. The ability to deliver therapeutic agents in a minimally invasive manner will also enhance clinical acceptance.

5. **Long-term Safety, Monitoring, and Ethics:** As regenerative therapies enter clinical trials, long-term safety monitoring becomes paramount. Addressing concerns regarding arrhythmogenicity, tumorigenicity, and immune complications will be critical to ensure regulatory approval and widespread adoption.[69] Moreover, ethical considerations surrounding gene editing and stem cell-derived products require global consensus to maintain public trust in the field.

6. **Lessons from Comparative Biology and Evolutionary Insights:** The regenerative success of species like zebrafish and axolotl underscores the importance of evolutionary biology in informing therapeutic design. Insights into the molecular cues driving scar-free healing, dedifferentiation, and cardiomyocyte proliferation in these species could inspire novel human therapies. Future research will likely focus on uncovering evolutionary "switches" that suppress regeneration in mammals and exploring whether they can be safely reactivated.

7. **Toward Clinical Reality:** The ultimate outlook is cautiously optimistic. Several ongoing early-phase clinical trials are already testing stem cell-derived cardiomyocytes, engineered tissue patches, and EV-based therapies in heart failure patients. If these interventions demonstrate efficacy without unacceptable risks, the next decade could see regenerative cardiology transition from experimental innovation to standard-of-care therapy.[70]

The next decade is poised to witness a paradigm shift in cardiology. The prospect of moving from disease management to functional cure through myocardial regeneration is no longer purely theoretical. With ongoing convergence of pharmacology, regenerative biology, and digital medicine, cardiac care may evolve from symptom palliation to structural and cellular repair. Although hurdles remain, the long-term vision is the transformation of heart failure from a progressive, irreversible condition into a treatable and potentially reversible disorder.

10. Conclusion

Cardiac remodelling and regeneration represent two intimately interconnected yet biologically distinct processes that determine the fate of the injured heart. Pathological remodelling, characterized by cardiomyocyte loss, maladaptive hypertrophy, fibrosis, and extracellular matrix disarray, remains the principal mechanism driving the progression of heart failure. Despite major advances in pharmacological and device-based interventions, current therapies are largely limited to slowing or partially reversing remodelling, without providing a definitive cure. The inability of the adult human heart to regenerate substantial numbers of cardiomyocytes after injury highlights the need for novel regenerative approaches that move beyond symptomatic management toward structural repair and functional restoration.

Recent progress in molecular cardiology, stem cell research, and tissue engineering has reinvigorated interest in the concept of cardiac regeneration. Discoveries related to cardiomyocyte proliferation, Hippo–YAP signalling, epigenetic reprogramming, and stem cell–derived cardiomyocytes have provided mechanistic insights into pathways that could be exploited for therapeutic benefit.

Additionally, extracellular vesicles, growth factor delivery, mRNA therapeutics, and engineered biomaterials have emerged as promising platforms to stimulate endogenous repair and improve myocardial integration. Such advances are reshaping our understanding of how the injured heart can be coaxed into regenerating functional tissue. Importantly, reverse remodelling and regeneration should not be viewed as separate goals but as complementary strategies. Effective therapies will likely involve a multimodal approach — attenuating pathological remodelling while simultaneously promoting cellular and structural regeneration. Integration of AI-driven diagnostics, multi-omics profiling, and precision medicine will be essential to tailor interventions to individual patients, ensuring maximum efficacy and safety.

Nonetheless, significant hurdles remain. The challenges of arrhythmogenic risks, immune incompatibility, ethical issues, and the high cost of regenerative therapies must be addressed before widespread clinical translation is possible. Large-scale, randomized clinical trials are required to establish long-term safety, durability, and cost-effectiveness. Moreover, interdisciplinary collaboration between cardiologists, molecular biologists, bioengineers, and data scientists will be pivotal to accelerate progress. In conclusion, while complete myocardial regeneration in humans remains an aspirational goal, the convergence of anti-remodelling therapies, regenerative biology, and digital health technologies is steadily transforming the treatment paradigm of heart failure. The future of cardiac medicine is likely to shift from disease management toward true repair and regeneration, offering the possibility of not only prolonging life but also restoring quality of life for millions of patients worldwide.

11. Source of Funding

None.

12. Conflict of Interest

None.

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Cite this article: Dubey S. Cardiac remodelling and regeneration: State of the science, translational pathways, and clinical outlook, *Indian J Clin Anat Physiol*. 2025;12(3):117.