Journal of Clinical and Biomedical Research ISSN: 4005-212X

Therapeutic Modulation of Failing Myocardium by Cardiac Glycosides: From Classic Inotropy to Modern Targets

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Abstract

Cardiac glycosides remain a unique pharmacological class that directly targets cardiomyocyte ion homeostasis and contractile machinery in heart failure, despite the rise of neurohormonal blockers and device therapy. Acting primarily via Na^+/K^+-ATPase inhibition, agents such as digoxin, digitoxin, and ouabain shift intracellular sodium–calcium balance, augment sarcoplasmic reticulum calcium load, and enhance systolic force without proportionally increasing myocardial oxygen consumption. Their impact extends beyond acute inotropy to include modulation of excitation–contraction coupling, neurohormonal activation, and myocardial remodeling. Experimental models demonstrate attenuation of hypertrophy, collagen deposition, and maladaptive changes in calcium-handling proteins with chronic digitoxin administration, while clinical and pediatric data suggest preserved ventricular volumes and reduced adverse remodeling in selected populations treated with digoxin. Nevertheless, narrow therapeutic index and arrhythmogenic risk constrain widespread use, prompting renewed interest in dose optimization and novel, tissue-selective Na^+/K^+-ATPase ligands. This review summarizes cellular mechanisms, structural remodeling effects, and clinical implications of cardiac glycosides in heart failure, highlighting their evolving therapeutic niche within contemporary multidrug regimens.

Keywords: cardiac glycosides, digoxin, myocardial remodeling, calcium handling, Na^+/K^+-ATPase, heart failure, excitation–contraction coupling

Introduction

Cardiac glycosides have been used for more than two centuries to treat congestive heart failure and certain supraventricular arrhythmias, primarily through a positive inotropic effect that strengthens myocardial contraction. Their canonical mechanism involves inhibition of the sarcolemmal Na^+/K^+-ATPase, leading to increased intracellular sodium, secondary reduction in Na^+–Ca^{2+} exchanger activity, and accumulation of intracellular calcium that augments contractile force. Despite the emergence of neurohormonal antagonists and device therapies that reduce mortality, cardiac glycosides retain a role in symptom relief and rate control in selected heart failure populations, especially when hypotension or renal dysfunction limits other therapies.[1][2][3][4][5]

Contemporary research revisits cardiac glycosides not only as inotropes but also as modulators of myocardial remodeling, calcium-handling proteins, and neurohormonal activation. Experimental data show that digitoxin can attenuate post-infarction heart failure, improve ventricular performance, and preserve sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2) and phospholamban phosphorylation, thereby stabilizing excitation–contraction coupling in failing myocardium. Clinical and translational studies suggest that digoxin may help preserve ventricular volumes and valve dimensions in infants with single-ventricle physiology, potentially linking classic inotropy with favorable structural remodeling. This article reviews how the therapeutic capabilities of cardiac glycosides on myocardial tissue extend from acute ionic effects to long-term structural and functional adaptations in heart failure.[6][7][4][8][9]

Methods

This narrative review synthesized experimental, translational, and clinical evidence regarding the effects of cardiac glycosides on myocardial tissue in heart failure. Primary sources included peer-reviewed articles and authoritative pharmacology and cardiology references focusing on Na^+/K^+-ATPase inhibition, calcium handling, ventricular remodeling, and clinical outcomes with digoxin, digitoxin, or ouabain. Studies were qualitatively compared to delineate converging mechanisms and clinically relevant myocardial effects. Emphasis was placed on mechanistic work in isolated cardiomyocytes and failing human myocardium, animal models of ischemic and volume-overload heart failure, and observational or interventional studies assessing structural and functional indices under chronic glycoside therapy.[10][3][7][4][8][11][9][1][6]

Cellular Mechanisms in Failing Myocardium

Cardiac glycosides bind to the extracellular domain of the Na^+/K^+-ATPase α-subunit in cardiomyocytes, inhibiting active extrusion of sodium and thereby elevating intracellular Na^+ concentration. The consequent reduction in the driving force for Na^+ entry through the Na^+–Ca^{2+} exchanger (NCX1) decreases calcium extrusion, increasing cytosolic and sarcoplasmic reticulum calcium content and amplifying systolic calcium transients. This results in greater binding of calcium to troponin C, enhanced actin–myosin cross-bridge cycling, and a net positive inotropic effect, which is especially valuable in dilated, hypocontractile ventricles characteristic of advanced heart failure. Recent work emphasizes that allosteric Na^+-dependent inactivation of NCX1, rather than mere changes in transmembrane sodium gradients, is essential for the inotropic action of digoxin, underscoring nuanced regulation of exchanger activity by cytosolic Na^+.[12][3][11][5][1]

Experimental data in cultured myocardial cells exposed to ouabain show that positive inotropy develops in parallel with inhibition of monovalent cation active transport and rises in intracellular Na^+ and Ca^{2+} within minutes. The onset and offset of the contractile response closely track Na^+/K^+-ATPase inhibition and recovery, respectively,

confirming a causal link between pump blockade, ionic shifts, and enhanced contraction. In failing human myocardium, ouabain increases peak twitch tension with only a moderate rise in calcium-related heat production and without compromising overall contraction economy, contrasting with isoproterenol, which augments calcium turnover at the cost of markedly reduced excitation–contraction coupling efficiency. This relatively efficient inotropic profile suggests that cardiac glycosides can strengthen contraction in failing hearts without proportional increases in energy expenditure, a potential advantage over cyclic AMP-dependent inotropes.[13][4][11][10]

Impact on Calcium-Handling Proteins and Excitation–Contraction Coupling

Beyond acute changes in intracellular ion concentrations, chronic exposure to cardiac glycosides influences proteins that govern calcium cycling in failing myocardium. In a rat model of myocardial infarction–induced heart failure, long-term digitoxin administration improved indices of cardiac remodeling and inotropism while preserving myocardial levels of key calcium-handling proteins, including SERCA2 and phosphorylated phospholamban. Untreated infarcted hearts showed decreased SERCA2 and phospholamban phosphorylation with increased Na^+–Ca^{2+} exchanger expression, a pattern that favors diastolic calcium overload and impaired relaxation, whereas digitoxin therapy mitigated these changes and supported more balanced calcium kinetics. Such modulation of calcium-handling proteins may stabilize systolic and diastolic function beyond the immediate Na^+/K^+-ATPase effect.[6]

In failing human ventricular tissue, ouabain's enhancement of twitch tension occurred without detrimental effects on cross-bridge energetics or recovery metabolism, suggesting that calcium delivery to the contractile apparatus was improved without increasing energy cost per unit of force. The moderate rise in excitation–contraction coupling–related heat with ouabain, compared to the large increase seen with isoproterenol, indicates a more economical recalibration of calcium cycling within the failing myocyte. Collectively, these findings support a model in which cardiac glycosides restore more favorable excitation–contraction coupling by boosting sarcoplasmic reticulum calcium content and normalizing calcium-handling protein expression and function, thereby enhancing contractility with relatively preserved energetic efficiency.[4][11][6]

Structural Remodeling of Myocardial Tissue

Experimental heart failure models show that cardiac glycosides influence not only cardiomyocyte contractility but also the structural remodeling of ventricular tissue. In rats with large myocardial infarctions, chronic digitoxin therapy attenuated congestive heart failure, improved ventricular performance, and reduced adverse remodeling, including decreases in collagen accumulation and cardiomyocyte nuclear volume—markers of fibrosis and cellular hypertrophy, respectively. These animals also had better pulmonary congestion profiles and preserved proteins involved in calcium kinetics, indicating a comprehensive impact on both structural and functional aspects

of the failing ventricle. Such data suggest that carefully titrated glycoside therapy can partially reverse or blunt maladaptive remodeling processes that exacerbate systolic dysfunction and diastolic stiffness.[6]

In human and pediatric settings, structural benefits are beginning to be characterized. In infants with hypoplastic left heart syndrome, digoxin use during the interstage period has been associated with preserved right ventricular volumes and tricuspid valve annulus area, implying less adverse remodeling of the single systemic ventricle. These echocardiographic findings offer a plausible mechanistic link between observed survival benefits and improved ventricular geometry under digoxin therapy, extending the drug's perceived role beyond symptomatic inotropy. Older data from chronic volume-overload models suggest that while digoxin can improve baroreflex function and preserve β-adrenoceptor responsiveness at the myocardial level, its capacity to fully prevent progressive remodeling may be modest, highlighting that structural protection may depend on disease substrate, dosing, and concomitant therapies.[7][8][9]

Neurohormonal and Electrophysiological Effects

Cardiac glycosides exert important neurohormonal effects that intersect with their myocardial actions in heart failure. Digoxin has been shown to reduce sympathetic outflow and modulate baroreflex sensitivity, thereby dampening neurohumoral activation that otherwise accelerates myocardial damage, promotes remodeling, and increases arrhythmic risk. Attenuation of β-adrenoceptor desensitization and partial restoration of myocardial adenylate cyclase responsiveness have been reported in chronic volume-overload models treated with digoxin, supporting the concept that glycosides may reset adrenergic signaling toward a more physiological range. These effects may indirectly help preserve myocardial performance and slow structural deterioration, complementing direct inotropic actions.[9][4]

Electrophysiologically, cardiac glycosides slow conduction through the atrioventricular node and can help control ventricular rate in atrial fibrillation, which is particularly beneficial in heart failure patients who are sensitive to tachycardia-induced worsening of systolic function. However, the same ionic mechanisms that increase inotropy also heighten cell excitability and can precipitate almost any type of arrhythmia at toxic concentrations, including ventricular tachyarrhythmias and conduction blocks. The narrow therapeutic index of glycosides therefore demands meticulous dosing and monitoring, especially in the context of renal impairment, drug–drug interactions, and electrolyte disturbances, which can shift the balance from beneficial myocardial effects to potentially lethal toxicity.[14][15][2][4]

Therapeutic Profiles of Different Cardiac Glycosides

The most clinically relevant cardiac glycosides—digoxin, digitoxin, and ouabain—share the core mechanism of Na^+/K^+-ATPase inhibition but differ in pharmacokinetics, tissue distribution, and the depth of mechanistic characterization in failing myocardium. Digoxin, with its renal excretion and intermediate half-life, is widely

used for chronic heart failure symptom relief and rate control, whereas digitoxin's longer half-life and hepatic metabolism have made it attractive in specific contexts, including certain European practices and experimental heart failure models. Ouabain, while less common in chronic therapy, has been extensively studied in isolated human myocardial preparations to dissect excitation–contraction coupling and energetic effects under controlled conditions.[2][11][5][1][10][13][4][6]

A comparison of their myocardial-related therapeutic profiles illustrates overlapping but distinct advantages: digoxin is best characterized clinically, digitoxin has compelling preclinical data on remodeling and calcium-handling protein preservation, and ouabain provides detailed mechanistic insight into efficient inotropy in failing human myocardium. These nuances suggest that tailoring glycoside choice and dosing to patient phenotype, co-morbidities, and concomitant treatments could optimize myocardial benefits while minimizing risk.[11][10][13][4][6]

Myocardial-Related Features of Major Cardiac Glycosides

Feature	Digoxin	Digitoxin	Ouabain
Primary clinical use	Chronic heart failure symptom relief and rate control in AF[2][4]	Less common; used in some chronic HF settings and European practice[6][4]	Mainly experimental; acute inotropy studies in failing myocardium[10][11]
Main myocardial mechanism	Na^+/K^+-ATPase inhibition, NCX1 modulation, ↑ Ca^{2+} transients[12][1][3]	Same core mechanism; chronic effects on Ca^{2+} proteins[6]	Na^+/K^+-ATPase inhibition; efficient inotropy in failing human tissue[10][11]
Remodeling impact	Association with preserved RV indices in single ventricle[7][8]	Attenuates post-MI HF, fibrosis, hypertrophy in rats[6]	Limited chronic data; mainly functional studies[10][11]
Calcium-handling protein effects	Indirect; improved Ca^{2+} cycling via ionic shifts[12][3][4]	Preserves SERCA2, phospholamban phosphorylation[6]	Alters Ca^{2+} cycling without worsening contraction economy[11]
Energetic efficiency of contraction	More economical than cAMP inotropes in practice[4][11]	Suggested by remodeling and function data[6]	Maintains contraction economy vs isoproterenol in failing myocardium[11]
Neurohormonal and autonomic effects	Sympatholytic, improved baroreflex function[4][9]	Less defined; likely similar class effects[6][4]	Primarily mechanical; neurohormonal impact less studied[11]

Clinical Implications and Evolving Role in Heart Failure

In the modern era of heart failure management, cardiac glycosides are no longer first-line mortality-reducing agents, but their myocardial effects can provide targeted benefits in carefully selected patients. Current practice leverages their ability to enhance contractility and control ventricular rate in atrial fibrillation, particularly in patients with low blood pressure or advanced symptoms despite optimized neurohormonal blockade, where additional inotropic support may improve functional

capacity. Observational data in pediatric single-ventricle populations indicate that digoxin use correlates with preserved ventricular geometry and improved interstage survival, supporting the idea that its myocardial actions can translate into meaningful clinical advantages beyond symptom relief.[8][2][7][4]

At the same time, concerns about arrhythmogenicity and toxicity emphasize the need for low-dose strategies that aim for modest, stable increases in intracellular calcium rather than maximal inotropy. Emerging mechanistic insights into NCX1 allosteric regulation, calcium-handling protein modulation, and energy-efficient excitation–contraction coupling suggest that future therapies may refine the "digitalis paradigm" by exploiting Na^+/K^+-ATPase signaling or isoform-selective ligands to recapitulate beneficial myocardial effects with lower pro-arrhythmic risk. For clinicians, understanding the depth of glycoside action on failing myocardium—from ionic fluxes to structural remodeling—can inform individualized decisions about when and how to integrate these agents into complex heart failure regimens.[15][14][12][4][11][6]

Discussion

The therapeutic capabilities of cardiac glycosides in heart failure arise from a layered interplay between ionic transport, calcium handling, tissue structure, and neurohormonal signaling within the failing myocardium. At the cellular level, inhibition of Na^+/K^+-ATPase elevates intracellular sodium, which in turn limits NCX-mediated calcium efflux, increases sarcoplasmic reticulum calcium load, and enhances systolic calcium transients, thereby restoring contractile force in dilated and hypocontractile ventricles. Newer evidence that Na^+-dependent inactivation of NCX1 is essential for digoxin's inotropic action refines the classic model and points to exchanger regulation as a key therapeutic node. In failing human myocardium, ouabain's ability to increase twitch tension without compromising contraction economy differentiates glycosides from cyclic AMP-dependent inotropes, which often exact an energetic penalty that may hasten disease progression.[3][5][12][1][4][11][6]

Equally important are the long-term effects of cardiac glycosides on myocardial remodeling and calcium-handling protein expression. Preclinical studies demonstrate that chronic digitoxin therapy can attenuate post-infarction heart failure, reduce fibrosis and hypertrophy, and preserve SERCA2 and phospholamban phosphorylation, suggesting that the myocardium adapts to sustained Na^+/K^+-ATPase modulation in a structurally favorable manner. Pediatric data linking digoxin to preserved right ventricular indices in single-ventricle physiology further support the notion that glycoside therapy may stabilize ventricular geometry and reduce adverse remodeling in selected clinical contexts. These findings contrast with earlier models of chronic volume overload, where digoxin did not fully prevent progressive remodeling despite hemodynamic benefits, underscoring the heterogeneity of heart failure substrates and the need to match therapy to underlying pathophysiology.[7][8][9][6]

Nevertheless, the narrow therapeutic window of cardiac glycosides remains a major constraint. The same elevation of intracellular calcium that underpins beneficial

inotropy can also increase triggered activity and re-entry susceptibility, giving rise to a spectrum of arrhythmias as concentrations approach toxic levels. Electrolyte disturbances, renal dysfunction, and polypharmacy common in heart failure amplify this risk, demanding careful titration, monitoring, and patient selection. Consequently, contemporary strategies favor low-dose digoxin aimed at modest increases in contractility and neurohormonal modulation rather than aggressive inotropic support, aligning with evidence that small, stable improvements in calcium cycling can be achieved without sharply increasing arrhythmic burden.[14][15][4]

Looking forward, mechanistic insights into Na^+/K^+-ATPase isoforms, NCX1 regulation, and calcium-handling protein networks offer opportunities to "decouple" the constructive myocardial effects of glycosides from their toxic potential. Development of partial agonists, biased ligands, or targeted delivery systems could enable selective engagement of cardioprotective signaling while limiting global ion pump inhibition. At the same time, better phenotyping of patients—using imaging, biomarkers, and perhaps genomic or proteomic profiles—might identify subgroups in whom the myocardial benefits of cardiac glycosides, such as improved contractile efficiency and attenuated remodeling, outweigh the risks. In this way, a traditionally "old" drug class could be repositioned as a precision tool within modern heart failure therapeutics, particularly where contractile reserve is low but oxygen supply is constrained.[12][11][6]

Conclusion

Cardiac glycosides occupy a distinctive therapeutic niche in heart failure by directly re-engineering the ionic and contractile behavior of failing myocardium while exerting broader influences on ventricular structure and neurohormonal activation. Through Na^+/K^+-ATPase inhibition and finely tuned modulation of calcium handling, these agents can restore systolic strength, support more economical excitation–contraction coupling, and, in selected settings, attenuate fibrotic and hypertrophic remodeling. Experimental and clinical data together portray cardiac glycosides not only as classic inotropes but also as subtle remodelers of myocardial tissue architecture and function. Harnessing these multifaceted capabilities safely will depend on precision dosing, vigilant monitoring, and continued translation of mechanistic discoveries into next-generation Na^+/K^+-ATPase–targeted therapies that preserve the heart's contractile advantage while minimizing arrhythmic risk.

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