



(RESEARCH ARTICLE)



TARGETING THE NEURO-CARDIAC AXIS IN HYPERTENSIVE HEART DISEASE: CARDIAC SYMPATHETIC DENERVATION AS A MECHANISTICALLY AND CLINICALLY DIRECTED STRATEGY TO PREVENT OR REVERSE CARDIAC REMODELING

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ABSTRACT

Objectives: Hypertensive heart disease (HHD) represents one of the most prevalent and devastating consequences of uncontrolled hypertension, characterized by progressive left ventricular hypertrophy (LVH), interstitial fibrosis, and diastolic dysfunction leading to heart failure with preserved ejection fraction (HFpEF). Sympathetic nervous system (SNS) overactivity has been identified as a central pathogenic mechanism linking sustained pressure overload to myocardial remodeling and impaired ventricular relaxation. This article proposes cardiac sympathetic denervation (CSD) as a mechanistically directed strategy to interrupt the maladaptive neuro-cardiac feedback loop in HHD and prevent or reverse cardiac remodeling.

Design: Conceptual hypothesis and narrative synthesis of translational and clinical evidence, integrating mechanistic pathways, preclinical data, and existing neuromodulation therapies to construct a mechanistic model and proposed experimental framework.

Setting: Not applicable; conceptual work based on published preclinical and clinical literature.

Participants: Not applicable; no human or animal subjects were directly enrolled. Proposed study populations are outlined for future experimental and clinical trials.

Interventions: Cardiac sympathetic denervation (surgical or catheter-based interruption of sympathetic efferent fibers from the stellate ganglia and upper thoracic chain), considered alongside other autonomic neuromodulatory interventions such as renal denervation (RDN), baroreflex activation therapy (BAT), and vagal nerve stimulation (VNS).

Primary and secondary outcome measures: This hypothesis paper outlines potential primary outcomes—including regression of left ventricular mass index and improvement in diastolic function—and secondary outcomes such as

changes in autonomic indices, neurohormonal biomarkers, and fibrosis imaging parameters, to be evaluated in future translational and clinical trials.

Results: No empirical trial data are presented. Drawing on translational evidence from ventricular arrhythmia management, RDN, BAT, and VNS, this work synthesizes support for the concept that selective interruption of cardiac sympathetic outflow can mitigate myocardial stress, suppress neurohormonal activation, and promote regression of pathological remodeling. A multiphase experimental and clinical framework is described to test this hypothesis.

Conclusions: Targeted CSD may serve as a mechanistically guided, disease-modifying strategy for patients with early or advanced HHD by restoring autonomic balance and reducing neurohormonal overload. Validation of this hypothesis through structured preclinical and clinical programs could establish CSD—potentially in combination with complementary autonomic interventions such as nocturnal lower-limb elevation—as a next-generation therapy to alter the natural trajectory toward HFpEF.

Keywords: Cardiac Sympathetic Denervation; Hypertensive Heart Disease; Left Ventricular Hypertrophy; Diastolic Dysfunction; Autonomic Modulation; Neuro-Cardiac Remodeling; Heart Failure with Preserved Ejection Fraction (Hfpef)

1 INTRODUCTION

1.1 Epidemiology and clinical significance

Hypertension remains the leading cause of cardiovascular morbidity and mortality globally, affecting over one billion individuals [1]. Chronic elevation in blood pressure imposes mechanical and neurohormonal stress on the myocardium, initiating a cascade of compensatory changes collectively referred to as hypertensive heart disease (HHD). These alterations include left ventricular hypertrophy (LVH), interstitial fibrosis, and reduced compliance, all of which culminate in impaired diastolic function [2]. Over time, this process predisposes patients to heart failure with preserved ejection fraction (HFpEF)—a condition that now accounts for nearly half of all heart failure cases and carries significant morbidity and mortality despite preserved systolic function [3].

While the hemodynamic burden of hypertension is well recognized, the autonomic imbalance that accompanies it—marked by sustained sympathetic overactivation and parasympathetic withdrawal—has emerged as a key determinant of disease progression [4, 5]. Heightened sympathetic activity increases cardiac afterload and promotes structural remodeling through both direct neurotoxic effects and neurohormonal activation of the renin–angiotensin–aldosterone system (RAAS) [6, 7].

1.2 Pathophysiologic role of sympathetic overactivity

The sympathetic nervous system (SNS) regulates cardiovascular homeostasis through intricate neural circuits involving central medullary centers, preganglionic thoracic neurons (T1–T5), and postganglionic fibers projecting via the stellate ganglia to the heart [8, 9]. In hypertension, chronic activation of these pathways results in excessive norepinephrine (NE) release at the myocardial synaptic cleft, contributing to cardiomyocyte hypertrophy, mitochondrial dysfunction, and interstitial fibrosis [4, 10].

Experimental and clinical studies have demonstrated elevated cardiac norepinephrine spillover rates in patients with HHD, correlating with LV mass index and diastolic dysfunction [11]. Moreover, microneurography and heart rate variability (HRV) analyses reveal increased muscle sympathetic nerve activity (MSNA) and diminished baroreflex sensitivity, both independent predictors of adverse cardiovascular outcomes [12–14].

1.3 Structural and molecular consequences

Sustained sympathetic stimulation leads to maladaptive neuro-cardiac remodeling, characterized by myocyte hypertrophy, collagen deposition, and extracellular matrix expansion. This process is mediated through multiple downstream mechanisms, including β_1 -adrenergic receptor overstimulation, activation of transforming growth factor-beta (TGF- β), and oxidative stress pathways [15–17]. The resultant increase in myocardial stiffness contributes to impaired relaxation and reduced ventricular compliance—core features of diastolic dysfunction [18].

At the microvascular level, sympathetic overactivity also contributes to endothelial dysfunction, vasoconstriction, and microvascular rarefaction, thereby reducing coronary flow reserve and perpetuating myocardial ischemia [19–21]. These changes reinforce a feed-forward loop wherein neurogenic, hemodynamic, and metabolic stresses collectively drive disease progression.

Limitations of current therapy

Although pharmacologic therapy remains the cornerstone of hypertension management, its efficacy in reversing established cardiac remodeling is modest. Agents targeting the RAAS—such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs)—partially mitigate hypertrophy and fibrosis but fail to normalize sympathetic drive [22, 23]. Beta-blockers reduce heart rate and myocardial oxygen demand but often do not suppress local cardiac sympathetic nerve activity sufficiently to reverse structural changes [24].

Device-based interventions such as renal denervation (RDN) and baroreflex activation therapy (BAT) have shown promising reductions in blood pressure and sympathetic tone, yet their direct cardiac effects remain variable [25, 26]. Consequently, cardiac-specific sympathetic modulation has emerged as an attractive target for addressing the residual risk associated with uncontrolled neurohormonal activation.

1.4 Hypothesis

This paper proposes that targeted cardiac sympathetic denervation (CSD)—achieved through thoracoscopic or catheter-based interruption of sympathetic efferent fibers arising from the stellate ganglia and upper thoracic chain—can prevent or reverse hypertensive cardiac remodeling by restoring autonomic balance and reducing neurohormonal overload.

Specifically, the hypothesis asserts that:

- In early-stage hypertensive heart disease, CSD attenuates neurogenic and hemodynamic stimuli driving left ventricular hypertrophy (LVH), thereby preventing fibrosis and diastolic dysfunction.
- In moderate-to-severe HHD, CSD reduces norepinephrine (NE) spillover, myocardial oxidative stress, and wall tension, thereby promoting reverse remodeling and improved diastolic compliance.
- Through chronic modulation of the neuro-cardiac reflex arc, CSD recalibrates baroreceptor sensitivity, suppresses RAAS activation, and stabilizes blood pressure variability—critical in preventing HFpEF progression.

This hypothesis is mechanistically grounded in the concept that the sympathetic nervous system is not merely a mediator but a primary driver of cardiac remodeling, and that targeted interruption at the cardiac level may yield benefits beyond systemic pharmacologic control.

2 METHODS

This article is structured as a conceptual, hypothesis-generating narrative review and mechanistic analysis. Existing preclinical and clinical data on sympathetic activation, hypertensive cardiac remodeling, and neuromodulatory therapies (including CSD, RDN, BAT, and VNS) are synthesized to construct a coherent neuro-cardiac model. Based on these mechanisms, a phased experimental and clinical framework is outlined to test the proposed role of CSD as a disease-modifying intervention in HHD. No original patient data were collected, and no formal systematic review or meta-analysis was performed.

2.1.1 Results: Conceptual Synthesis and Mechanistic Model

2.1.1.1 Mechanistic basis and literature review

2.1.1.1.1 The neuro-cardiac axis in hypertension

The heart receives dense sympathetic innervation originating from preganglionic neurons in the intermediolateral columns of the spinal cord (T1–T5) that synapse within the stellate and middle cervical ganglia before projecting postganglionic fibers to the myocardium and coronary vasculature [8, 9]. In hypertensive states, heightened excitatory afferent input from cardiac and vascular baroreceptors enhances central sympathetic outflow via medullary circuits, resulting in sustained NE release at cardiac nerve terminals [5, 7].

Chronic sympathetic excitation increases norepinephrine spillover, leading to β_1 -adrenergic receptor downregulation, desensitization of G-protein signaling, and altered calcium handling in cardiomyocytes [6, 27]. Simultaneously, it promotes oxidative stress and inflammation through the upregulation of NADPH oxidase and nuclear factor κ B (NF- κ B) pathways [15, 16]. These molecular changes trigger mitochondrial dysfunction, myocyte apoptosis, and fibroblast activation—hallmarks of pathologic remodeling.

Furthermore, sympathetic overdrive impairs the arterial baroreflex, a central mechanism that maintains cardiovascular homeostasis [13]. Baroreflex desensitization in chronic hypertension amplifies blood pressure variability and blunts the normal inhibitory feedback to sympathetic efferent neurons, thereby perpetuating neurohormonal activation [19].

2.2 Molecular pathways linking sympathetic activation to cardiac remodeling

Persistent NE exposure initiates a series of intracellular events that transition adaptive hypertrophy into maladaptive fibrosis. β -adrenergic receptor overstimulation increases cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activity, leading to phosphorylation of calcium-handling proteins and prolonged cytosolic calcium transients [15]. This calcium overload, in turn, activates calcineurin–NFAT signaling, promoting hypertrophic gene expression [28].

On the structural level, sympathetic hyperactivity upregulates TGF- β 1, collagen I/III synthesis, and lysyl oxidase expression, resulting in enhanced crosslinking of the extracellular matrix and reduced myocardial compliance [18, 20]. Additionally, oxidative stress and angiotensin II act synergistically to stimulate fibroblast proliferation and impair titin phosphorylation, further increasing diastolic stiffness [16, 17].

These processes are collectively known as neurogenic fibrosis—a distinct pathologic phenotype seen in hypertensive patients with elevated plasma or myocardial NE levels [4, 29].

2.3 Evidence from cardiac sympathetic denervation (CSD)

CSD was first developed as a surgical intervention for refractory ventricular arrhythmias and electrical storm, where excessive sympathetic input contributes to malignant reentry and triggered activity. Bilateral stellate ganglionectomy has been shown to significantly reduce arrhythmic burden and improve survival in these populations [30, 31]. Interestingly, follow-up imaging and histologic studies in these patients revealed not only electrical stabilization but also reverse structural remodeling, including improved ventricular function and reduced fibrosis [32].

In animal models of hypertensive cardiomyopathy, selective left stellate ganglionectomy decreased LV mass, reduced collagen deposition, and normalized expression of TGF- β 1 and connective tissue growth factor (CTGF) without significantly altering systemic blood pressure [33]. These findings suggest that CSD exerts local myocardial benefits independent of hemodynamic unloading.

Emerging data from advanced heart failure cohorts further demonstrate that cardiac sympathetic modulation can improve autonomic balance and baroreflex sensitivity, thereby stabilizing hemodynamics and reducing arrhythmic risk [34].

2.4 Evidence from renal denervation and other neuromodulatory therapies

The success of renal denervation (RDN) in resistant hypertension provides additional mechanistic validation for sympathetic modulation. By ablating renal efferent and afferent fibers, RDN reduces central sympathetic outflow and circulating catecholamines, resulting in both blood pressure reduction and regression of LVH [35, 36]. Cardiovascular magnetic resonance (CMR) studies following RDN have demonstrated decreases in left ventricular mass index (LVMI) and extracellular volume (ECV), along with improved diastolic parameters [35, 37].

Similarly, baroreflex activation therapy (BAT) and vagal nerve stimulation (VNS) have shown reductions in sympathetic drive, improvements in HRV indices, and enhanced myocardial performance in both hypertensive and heart failure populations [11, 26]. Collectively, these findings underscore that autonomic modulation—whether renal, cardiac, or baroreceptor-based—has structural implications on the myocardium, reinforcing the premise that sympathetic interruption can be disease-modifying.

2.5 Structural, functional, and molecular assessment tools

Quantifying the effects of sympathetic modulation requires multimodal assessment. Modern cardiac imaging techniques, including T1 and T2 mapping, extracellular volume fraction (ECV) quantification, and global longitudinal strain (GLS), provide sensitive markers of fibrosis, hypertrophy, and relaxation [38]. ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) scintigraphy enables direct visualization of cardiac sympathetic innervation, correlating reduced uptake with increased NE turnover and disease severity [39].

Additionally, circulating biomarkers such as NT-proBNP, galectin-3, and soluble ST2 reflect myocardial stretch and fibrosis burden, while plasma NE and angiotensin II levels provide indices of autonomic and RAAS activation [20, 22]. Integration of these modalities offers a comprehensive framework for evaluating the physiologic and structural outcomes of CSD interventions.

2.6 Mechanistic model of cardiac sympathetic denervation in hypertensive heart disease

Hypertensive heart disease arises through a complex interplay between mechanical overload, neurohormonal dysregulation, and structural remodeling. Chronic arterial hypertension initiates increased wall stress, leading to compensatory concentric hypertrophy. Over time, the accompanying rise in sympathetic nervous system (SNS) activity—both systemic and local—amplifies cardiac metabolic demand, oxygen consumption, and wall tension [4, 40].

Persistent sympathetic efferent stimulation from the stellate ganglia and thoracic sympathetic chain results in elevated norepinephrine (NE) release at the myocardial synapse, which triggers a cascade of pathophysiologic events [6, 15]:

- **Neurohumoral activation:** NE stimulates β_1 -adrenergic receptors, leading to increased cAMP/PKA signaling, calcium overload, and activation of the calcineurin–NFAT pathway. This enhances hypertrophic gene expression and reduces contractile efficiency [28].
- **Oxidative stress and inflammation:** Chronic adrenergic stimulation activates NADPH oxidase and promotes reactive oxygen species (ROS) generation, which in turn triggers nuclear factor κ B (NF- κ B) and downstream inflammatory mediators [16, 17].
- **Fibrotic remodeling:** Excess NE and angiotensin II synergistically activate transforming growth factor-beta (TGF- β 1), connective tissue growth factor (CTGF), and collagen I/III expression, leading to extracellular matrix (ECM) expansion and myocardial stiffness [18, 20].
- **Diastolic dysfunction:** Accumulation of interstitial collagen, altered titin phosphorylation, and microvascular rarefaction impair ventricular relaxation, precipitating HFpEF phenotypes [3, 19].
- This cascade creates a self-sustaining neuro-cardiac loop, where sympathetic excitation and cardiac remodeling reinforce each other.

Cardiac sympathetic denervation (CSD) disrupts this maladaptive loop by directly ablating or inhibiting sympathetic efferent fibers projecting to the myocardium from the stellate ganglia and upper thoracic sympathetic chain (T1–T5) [8, 32]. Mechanistically, CSD results in:

- Reduced norepinephrine spillover, mitigating β -adrenergic overstimulation and calcium overload.
- Downregulation of TGF- β 1 and collagen synthesis, reducing myocardial fibrosis.
- Decreased activation of the renin–angiotensin–aldosterone system (RAAS) via diminished sympathetic renal drive, lowering circulating angiotensin II.
- Improved baroreflex sensitivity and heart rate variability (HRV), indicating autonomic rebalancing.
- Reduced wall stress, enabling regression of hypertrophy and improved diastolic compliance.

These cumulative effects suggest that CSD acts both locally (at the cardiac level) and systemically (via autonomic reconfiguration) to reverse the structural and molecular sequelae of hypertension.

3 EXPERIMENTAL AND CLINICAL FRAMEWORK

3.1 Phase I: preclinical mechanistic studies

Objective

Characterize molecular and hemodynamic effects of selective CSD in hypertensive animal models.

3.2 Design

- Models: Spontaneously hypertensive rats (SHR) and Dahl salt-sensitive rats.
- Intervention: Unilateral (left) and bilateral stellate ganglionectomy or chemical sympathectomy.
- Endpoints:
 - Changes in left ventricular mass (LV mass index).
 - Myocardial NE concentration and β_1 -receptor density.
 - Expression of TGF- β 1, CTGF, collagen I/III, and oxidative stress markers (4-HNE, NOX2).
 - Assessment of fibrosis using histology and T1/T2 mapping MRI.
 - Autonomic indices (baroreflex sensitivity, HRV).

3.3 Expected outcome

CSD will reduce myocardial NE and fibrosis markers independent of systemic blood pressure change, confirming a local anti-fibrotic mechanism.

3.4 Phase II: pilot human feasibility study

3.4.1 Population

- Adults aged 30–75 years with essential hypertension ($\geq 140/90$ mmHg) and early diastolic dysfunction ($E/e' > 10$, $LVEF \geq 50\%$).
- Exclusion: Secondary hypertension, ischemic heart disease, advanced HFpEF, or recent arrhythmic events.

3.4.2 Intervention

- Procedure: Minimally invasive thoracoscopic left CSD targeting the stellate and upper thoracic sympathetic ganglia (T2–T4).
- Comparator: Sham thoracoscopic procedure with identical pre/post-operative management.
- Duration: 12-month follow-up with imaging and biomarker evaluation at baseline, 6 months, and 12 months.

3.4.3 Primary endpoints

- Change in left ventricular mass index (LVMI) measured by cardiac MRI (CMR).
- Improvement in diastolic function indices (E/e' , left atrial volume index, GLS).

3.4.4 Secondary endpoints

- 24-hour ambulatory blood pressure monitoring (ABPM).
- Heart rate variability (HRV) and baroreflex sensitivity (BRS).
- Circulating plasma NE, angiotensin II, NT-proBNP, and galectin-3 levels.
- Safety and procedure-related complications.

3.4.5 Expected results

Compared to control, the CSD group is expected to exhibit:

- $\geq 10\%$ reduction in LVMI.
- Significant improvement in diastolic relaxation (E/e' decrease by ≥ 2 units).
- Reduction in sympathetic and neurohormonal biomarkers.
- Enhanced autonomic modulation (increased HRV and BRS).

3.5 Phase III: randomized multicenter trial

3.5.1 Design

Population: Patients with established HHD or HFpEF ($LVEF \geq 50\%$, evidence of concentric LVH).

Intervention: Catheter-based percutaneous CSD using high-frequency ultrasound or ethanol ablation via the left cardiac sympathetic plexus (experimental arm) vs optimized medical therapy (control arm).

Follow-up: 24 months.

3.5.2 Primary outcomes

- Composite of LVH regression and diastolic improvement (E/e' reduction, LA strain normalization).
- Changes in CMR-based extracellular volume (ECV).
- Functional capacity improvement (6-minute walk test, VO_2 max).

3.5.3 Secondary outcomes

- Reduction in hospitalization for heart failure or hypertensive crisis.
- Autonomic balance markers (plasma NE, HRV indices).
- Safety profile and procedural reproducibility.

3.6 Statistical considerations

- Target sample size: 200 participants (1:1 allocation).
- Primary endpoint effect size assumption: 15% reduction in LVMI with 80% power and $\alpha = 0.05$.
- Interim analysis at 12 months for efficacy and safety.

3.7 Mechanistic biomarker integration

In all study phases, multimodal integration of imaging, neurohormonal, and molecular data will be essential to establish mechanistic correlation. For instance:

- T1 mapping and ECV quantification for fibrosis regression.
- ¹²³I-MIBG scintigraphy to assess sympathetic reinnervation or suppression.
- Biochemical markers (galectin-3, soluble ST2, NE, renin activity) to quantify neurohormonal suppression.
- Heart rate variability (HRV) metrics to evaluate autonomic rebalancing.

4 DISCUSSION

4.1 Beyond pharmacology: targeting the neuro-cardiac interface

Current management of hypertensive heart disease relies primarily on pharmacologic suppression of neurohormonal activation through renin–angiotensin–aldosterone system (RAAS) and β -adrenergic blockade. Although these therapies provide symptomatic relief and slow disease progression, they fail to normalize residual sympathetic overdrive—particularly local cardiac efferent activity [4, 22].

Cardiac sympathetic denervation represents a mechanistically distinct and potentially disease-modifying approach by directly disrupting efferent sympathetic signaling at the level of the myocardium. By attenuating norepinephrine spillover and reducing wall stress, CSD could complement pharmacologic therapies in a multimodal regimen aimed at neurohormonal recalibration rather than merely hemodynamic control.

4.2 Integration with complementary autonomic interventions

The neuro-cardiac remodeling process in hypertension is multifactorial, driven by both neural and hemodynamic components. Interventions that modulate autonomic tone can complement CSD by addressing residual sympathetic overactivity and enhancing parasympathetic function.

Adjunctive strategies such as baroreflex activation therapy, vagal nerve stimulation, and renal denervation have shown promise in reducing central sympathetic output, improving heart rate variability, and attenuating left ventricular hypertrophy [11, 26, 36]. These modalities act through different neuroanatomical pathways but share a unifying goal: restoration of autonomic balance and baroreflex sensitivity.

In this context, CSD can serve as a core neural intervention that directly reduces cardiac sympathetic efferent activity, while other neuromodulatory therapies target afferent and central reflex pathways. Integrating these modalities—either sequentially or concurrently—may yield additive benefits, resulting in sustained hemodynamic stability, enhanced cardiac compliance, and delayed progression to HFpEF. Future investigations should assess combined autonomic modulation protocols, focusing on objective endpoints such as 24-hour ambulatory blood pressure variability, plasma norepinephrine levels, and baroreflex sensitivity indices to determine optimal sequencing, safety, and long-term efficacy of these synergistic approaches.

4.3 Translational and clinical research pathway

The translational development of CSD for HHD will require a stepwise evidence chain:

- Mechanistic validation using molecular and imaging biomarkers (TGF- β 1, MIBG, LVMI).
- Pilot feasibility trials confirming procedural safety and proof-of-concept effects.
- Multicenter randomized studies assessing long-term functional and mortality benefits.
- Adjunctive autonomic therapies, such as nocturnal lower-limb elevation (LLE) or baroreflex pacing, to amplify neural reconditioning.

These studies should prioritize quantitative autonomic indices—baroreflex sensitivity (BRS), heart rate variability (HRV), and plasma norepinephrine—as primary mechanistic endpoints to demonstrate true autonomic restoration.

4.4 Ethical and safety considerations

As with all invasive neuromodulatory therapies, the ethical justification for CSD depends on demonstrating that its benefits outweigh procedural risks. Thoracoscopic and catheter-based CSD techniques are minimally invasive but may carry risks of Horner's syndrome, pneumothorax, or postoperative neuropathic pain [30, 32].

Rigorous preclinical validation, standardized surgical techniques, and long-term monitoring of autonomic and cardiac parameters are necessary. Furthermore, patient selection should focus on those with demonstrable sympathetic hyperactivity or refractory hypertensive remodeling not responsive to pharmacotherapy.

List of abbreviations

- ABPM – Ambulatory Blood Pressure Monitoring
- ACE – Angiotensin-Converting Enzyme
- BAT – Baroreflex Activation Therapy
- BRS – Baroreflex Sensitivity
- CMR – Cardiac Magnetic Resonance
- CSD – Cardiac Sympathetic Denervation
- ECM – Extracellular Matrix
- ECV – Extracellular Volume
- GLS – Global Longitudinal Strain
- HFpEF – Heart Failure with Preserved Ejection Fraction
- HHD – Hypertensive Heart Disease
- HRV – Heart Rate Variability
- LA – Left Atrium
- LV – Left Ventricle
- LVH – Left Ventricular Hypertrophy
- LVMI – Left Ventricular Mass Index
- MIBG – Metaiodobenzylguanidine
- NE – Norepinephrine
- NT-proBNP – N-terminal pro B-type Natriuretic Peptide
- RAAS – Renin–Angiotensin–Aldosterone System
- RDN – Renal Denervation
- ROS – Reactive Oxygen Species
- SNS – Sympathetic Nervous System
- TGF- β – Transforming Growth Factor Beta
- VNS – Vagal Nerve Stimulation

5 CONCLUSION

Hypertensive heart disease remains a leading contributor to cardiovascular morbidity and mortality. Central to its progression is the maladaptive activation of the sympathetic nervous system, which perpetuates a cycle of neurohormonal, mechanical, and structural remodeling.

This paper proposes that cardiac sympathetic denervation—by interrupting this maladaptive neuro-cardiac loop—may serve as a disease-modifying strategy for preventing or reversing hypertensive cardiac remodeling. Unlike systemic pharmacologic modulation, CSD targets the pathological substrate directly at the cardiac level, thereby restoring autonomic equilibrium, improving myocardial compliance, and potentially delaying the onset of HFpEF.

When combined with complementary non-invasive strategies such as nocturnal lower-limb elevation to enhance baroreflex sensitivity and vagal tone, CSD could form the foundation of a next-generation autonomic therapy paradigm in hypertension—integrating neural and hemodynamic control to achieve true cardiovascular remodeling reversal.

Article Summary

- Proposes cardiac sympathetic denervation (CSD) as a mechanistically guided intervention for hypertensive cardiac remodeling.
- Integrates neural and structural pathways underlying sympathetic overactivity in hypertensive heart disease (HHD).
- Synthesizes translational evidence from neuromodulation therapies, including CSD, baroreflex activation therapy (BAT), renal denervation (RDN), and vagal nerve stimulation (VNS).
- Outlines a mechanistic model and phased trial framework for disease modification in early and established HHD.
- Suggests future research directions linking autonomic restoration and complementary interventions (such as nocturnal lower-limb elevation) to myocardial recovery and prevention of HFpEF.

Strengths

- Provides a unified mechanistic model linking sympathetic overactivity, neurohormonal activation, and hypertensive cardiac remodeling.
- Integrates evidence from multiple neuromodulatory modalities (CSD, RDN, BAT, VNS) to support the plausibility of autonomic-targeted disease modification.
- Outlines a concrete, phased experimental and clinical framework that can directly guide future translational research.

Limitations

- The manuscript is conceptual and hypothesis-driven, without original empirical data.
- Proposed study designs and effect sizes are illustrative and require refinement using formal pilot data and feasibility assessments.
- Potential procedural risks, patient selection criteria, and cost-effectiveness considerations are discussed only at a high level and will need detailed evaluation in future work.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author declares no competing interests.

Author Contributions

Tilahun Senbeto conceptualized the hypothesis, conducted the literature review, developed the mechanistic model, integrated the lower-limb elevation concept, and wrote and revised the full manuscript.

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