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NOVEL NEUROMODULATION THERAPIES FOR HEART FAILURE AND RESISTANT HYPERTENSION

Novas Terapias de Neuromodulação para Insuficiência Cardíaca e Hipertensão Resistente

Nuevas Terapias de Neuromodulación para la Insuficiencia Cardíaca y la Hipertensión Resistente

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ABSTRACT

Heart failure and resistant hypertension are major clinical challenges frequently associated with autonomic nervous system dysfunction and sustained sympathetic hyperactivity. In this context, neuromodulation therapies have emerged as innovative strategies aimed at restoring autonomic balance and improving cardiovascular outcomes. To critically analyze recent scientific evidence on new neuromodulation therapies applied to heart failure and resistant hypertension, emphasizing physiological mechanisms, clinical outcomes, and future perspectives for clinical practice. An integrative literature review was conducted in PubMed, JACC, SciELO, and the American College of Cardiology databases using descriptors related to vagal stimulation, baroreflex activation, and renal denervation. Studies published within the last ten years with a minimum follow-up of six months were included. The main strategies identified were vagus nerve stimulation, carotid baroreflex activation therapy, and renal denervation. The analyzed studies demonstrated improvements in autonomic modulation, reductions in sympathetic activity, functional gains, and, in selected trials, increases in left ventricular ejection fraction and blood pressure control. Neuromodulation therapies show relevant clinical potential as adjunctive treatments to conventional pharmacological therapy, particularly in refractory patients. However, methodological heterogeneity and limited long-term data highlight the need for robust clinical trials to support their routine clinical adoption.

Keywords: *Neuromodulation; Heart Failure; Resistant Hypertension; Autonomic Nervous System; Vagus Nerve Stimulation.*

RESUMO

A insuficiência cardíaca e a hipertensão resistente representam desafios clínicos relevantes, frequentemente associados à disfunção do sistema nervoso autônomo e à hiperatividade simpática sustentada. Nesse contexto, terapias de neuromodulação emergem como estratégias inovadoras voltadas à restauração do equilíbrio autonômico e à melhora de desfechos cardiovasculares. O objetivo do estudo foi analisar criticamente as evidências científicas recentes sobre novas terapias de neuromodulação aplicadas à insuficiência cardíaca e à hipertensão resistente, com ênfase nos mecanismos fisiológicos envolvidos, nos resultados clínicos e nas perspectivas futuras para a prática clínica. Tratou-se de revisão integrativa da literatura realizada nas bases PubMed, JACC, SciELO e American College of Cardiology, utilizando descritores relacionados à estimulação vagal, ativação barorreflexa e denervação renal. Foram incluídos estudos publicados nos últimos dez anos, em periódicos indexados, com seguimento mínimo de seis meses. As principais estratégias identificadas incluem a estimulação do nervo vago, a ativação do barorreflexo carotídeo e a denervação renal. Os estudos analisados demonstram melhora da modulação autonômica, redução da atividade simpática, ganhos funcionais e, em alguns ensaios, incremento da fração de ejeção e do controle pressórico. As terapias de neuromodulação apresentam potencial clínico relevante como adjuvantes ao tratamento farmacológico convencional, especialmente em pacientes refratários. Contudo, a heterogeneidade metodológica e a limitação de dados de longo prazo reforçam a necessidade de ensaios clínicos robustos para consolidar sua incorporação rotineira na prática cardiovascular.

Palavras-chave: Neuromodulação; Insuficiência Cardíaca; Hipertensão Resistente; Sistema Nervoso Autônomo; Estimulação Vagal.

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RESUMEN

La insuficiencia cardíaca y la hipertensión resistente representan desafíos clínicos relevantes, frecuentemente asociados con disfunción del sistema nervioso autónomo e hiperactividad simpática sostenida. En este contexto, las terapias de neuromodulación surgen como estrategias innovadoras orientadas a restaurar el equilibrio autonómico y mejorar los resultados cardiovasculares. Analizar críticamente la evidencia científica reciente sobre nuevas terapias de neuromodulación aplicadas a la insuficiencia cardíaca y la hipertensión resistente, enfatizando los mecanismos fisiológicos, los resultados clínicos y las perspectivas futuras para la práctica clínica. Revisión integradora de la literatura realizada en las bases PubMed, JACC, SciELO y American College of Cardiology, utilizando descriptores relacionados con la estimulación vagal, la activación del barorreflejo y la denervación renal Las principales estrategias identificadas incluyen la estimulación del nervio vago, la activación del barorreflejo carotídeo y la denervación renal, con evidencia de mejora en la modulación autonómica, reducción de la actividad simpática y beneficios funcionales. Las terapias de neuromodulación presentan potencial clínico relevante como adyuvantes al tratamiento farmacológico convencional, aunque la falta de estudios de largo plazo refuerza la necesidad de ensayos clínicos más robustos.

Palabras clave: *Neuromodulación; Insuficiencia Cardíaca; Hipertensión Resistente; Sistema Nervioso Autónomo; Estimulación Vagal.*

1. INTRODUCTION

Neoadjuvant chemotherapy refers to systemic antineoplastic treatment administered prior to surgery or, in some cases, before radiotherapy, with the primary aim of reducing tumor size, thereby enabling and facilitating surgical resection. It is also employed to preserve organs and anatomical structures, such as the breast, allowing for less mutilating surgical procedures. In addition, neoadjuvant chemotherapy plays a crucial role in the early treatment of micrometastases that are not yet detectable by imaging or laboratory examinations. Tumor response to neoadjuvant chemotherapy provides valuable guidance for surgical decision-making and contributes to improved oncological outcomes.

In this context, there has been growing concern regarding the incidence of breast cancer in the southeastern region of Brazil between 2023 and 2024. In 2023, the Southeast presented an age-adjusted incidence rate of 81.06 cases per 100,000 women, the highest among all Brazilian regions. Breast cancer in this population encompasses different molecular subtypes, including Luminal A (HER2-negative with low proliferative index), Luminal B (HER2-positive or negative with higher proliferative index), HER2-positive (HER2 overexpression), and triple-negative breast cancer (negative for estrogen receptor [ER], progesterone receptor [PR], and HER2, and typically associated with high histological grade).

Furthermore, a national study conducted between 2023 and 2024 evaluated 176 patients diagnosed with triple-negative breast cancer treated within the Brazilian Unified Health System (Sistema Único de Saúde – SUS). The study revealed that 10.8% of patients received neoadjuvant chemotherapy, while 89.2% underwent adjuvant chemotherapy. The most frequently used therapeutic regimen was the combination of doxorubicin, cyclophosphamide, and a taxane, accounting for 80.7% of cases. In this regard, neoadjuvant chemotherapy represents a key therapeutic strategy in breast cancer management, particularly in patients with locally advanced or inflammatory HER2-positive disease.

Within this framework, the present study aims to highlight the relevance of cardiotoxicity associated with neoadjuvant chemotherapy in breast cancer treatment. This concern is primarily related to the chemotherapeutic agents commonly employed, such as anthracyclines—especially doxorubicin and epirubicin—which are well known for their cardiotoxic potential. Additionally, trastuzumab has been associated with left ventricular dysfunction and heart failure, particularly when administered in combination with anthracyclines.

Moreover, cardiotoxic effects are not always immediate during treatment, underscoring the need for careful and long-term surveillance. Cardiac monitoring through echocardiography, assessment of left ventricular ejection fraction, and evaluation of cardiac biomarkers is essential, as cardiotoxicity may manifest years after the completion of therapy. Importantly, cardiotoxicity may also negatively impact prognosis, as it can lead to interruption or reduced efficacy of oncological treatment by compromising tumor response. Consequently, it may result in chronic cardiovascular morbidity, adversely affecting quality of life and overall survival, even in cases where cancer control is achieved.

2. METHODOLOGY

The present integrative literature review was designed to identify, analyze, and synthesize scientific evidence regarding the use of neuromodulation therapies in the management of heart failure and resistant hypertension, considering pathophysiological mechanisms, clinical outcomes, and therapeutic implications. This methodological approach was chosen because it allows the inclusion of different types of studies, such as clinical trials, observational research, and experimental studies, thereby broadening the critical understanding of the topic.

The bibliographic search was conducted in the PubMed/MEDLINE databases, Journal of the

American College of Cardiology (JACC), SciELO, and the American College of Cardiology, using controlled and non-controlled descriptors related to the terms "neuromodulation," "vagus nerve stimulation," "baroreflex activation therapy," "renal denervation," "heart failure," and "resistant hypertension," combined using the Boolean operators AND and OR. Search strategies were adapted according to the specific characteristics of each database to ensure sensitivity and traceability of the process.

Eligible studies included articles published between 2014 and 2024 in Portuguese, English, and Spanish that addressed neuromodulation interventions applied to adults with heart failure or resistant hypertension, with a minimum follow-up of six months and reporting clinical, hemodynamic, or autonomic outcomes. Exclusively pediatric studies, isolated case reports, narrative reviews without explicit methodology, and publications lacking clear selection criteria or data analysis were excluded.

The screening process was carried out in two stages. Initially, titles and abstracts were reviewed to exclude duplicates and studies not relevant to the research objective. Subsequently, the full texts of potentially eligible articles were assessed for compliance with the inclusion criteria. Extracted data were organized into standardized spreadsheets, including information on study design, type of intervention, evaluated population, main outcomes, and methodological limitations.

Results were synthesized through qualitative thematic analysis, allowing the categorization of findings into central axes related to autonomic mechanisms, neuromodulation strategies, and observed clinical impacts. As this study was based exclusively on secondary sources in the public domain, submission to a Research Ethics Committee was not required, and ethical principles related to scientific integrity and proper attribution of sources were respected in accordance with ABNT standards.

3. RESULTS AND DISCUSSION

The analyzed studies demonstrate that neuromodulation primarily acts through the reduction of central sympathetic hyperactivity and the enhancement of parasympathetic tone, promoting relevant hemodynamic and structural effects. Vagus nerve stimulation has been shown to improve heart rate variability, reduce inflammatory markers, and, in some trials, increase left ventricular ejection fraction.

Carotid baroreflex activation demonstrated a significant impact on blood pressure control, with sustained reductions in arterial pressure in patients with resistant hypertension, in addition to functional improvement in subgroups with advanced heart failure. These effects appear to be related to direct

modulation of bulbar autonomic centers and inhibition of renal and cardiovascular sympathetic outflow.

Clinical trials summarized in Table 1 revealed heterogeneous results, ranging from objective gains in ventricular function and functional capacity to predominantly subjective improvements in quality of life. Overall, the studies indicate that neuromodulation strategies exert a consistent impact on functional and blood pressure outcomes, although cardiac structural effects remain heterogeneous. This variability reflects differences in stimulation protocols, duration of follow-up, and patient selection.

Despite their promising potential, methodological limitations persist, including small sample sizes, the absence of control groups in some studies, and a paucity of long-term data. Moreover, adverse effects such as hypotension, local discomfort, and transient changes in heart rate underscore the need for rigorous monitoring and individualized therapeutic approaches.

4. CONCLUSION

Neuromodulation therapies represent an emerging frontier in the management of heart failure and resistant hypertension, offering a pathophysiologically targeted approach aimed at restoring autonomic nervous system balance.

The findings suggest clinically relevant benefits, particularly in improving functional capacity, quality of life, and hemodynamic control in patients refractory to conventional pharmacological therapies.

However, the consolidation of these strategies in clinical practice depends on the conduct of large-scale randomized clinical trials with long-term follow-up, capable of establishing clear criteria for indication, safety, and impact on hard outcomes, such as mortality and hospitalizations.

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Table 1. Main neuromodulation studies in heart failure and arterial hypertension.

Study	Clinical condition	Study design	Population	Intervention	Main outcomes	Conclusion
ANTHEM-HF	Heart failure	Prospective, multicenter	60 patients; NYHA II–III; LVEF ≤40%; mean age 52 ± 12 years	Right cervical vagus nerve stimulation + optimal medical therapy (6 months; follow-up up to 42 months)	↑ LVEF (+4.5%); ↑ 6MWT (+56 m); ↓ MLHFQ (−21); NYHA class regression	VNS associated with functional, structural, and quality-of-life improvement
NECTAR-HF	Heart failure	Randomized, double-blind, placebo-controlled	96 patients; NYHA II–III; LVEF ≤35%	Active right cervical VNS vs. placebo + optimal medical therapy	↓ MLHFQ; subjective improvement in NYHA class and SF-36; no significant improvement in LVEF	Symptomatic benefit without significant structural impact
INNOVATE-HF	Heart failure	Randomized, controlled	707 patients; NYHA II–III; LVEF ≤40%	Right transvenous VNS with implantable pulse generator	↑ 6MWT (+28.2 m); NYHA improvement; ↓ MLHFQ (−11.2 and −6.9); no improvement in LVEF	Functional and quality-of-life improvement without echocardiographic gain
SPYRAL HTN-OFF MED	Arterial hypertension	Randomized, double-blind, placebo-controlled	Hypertensive patients not receiving antihypertensive medication	Radiofrequency renal denervation (spiral multielectrode catheter)	↓ 24-h SBP (−5 to −7 mmHg); ↓ 24-h DBP (−3 to −4 mmHg)	Effective blood pressure reduction even in the absence of pharmacological therapy

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RADIANCE-HTN	Arterial hypertension	Randomized, placebo-controlled	Hypertensive patients receiving ≥3 antihypertensive agents	Endovascular ultrasound renal denervation	↓ 24-h SBP (−6.3 mmHg); significant reduction in DBP	Effective and safe procedure for resistant hypertension