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SINUS NODE SYNDROME: CONTEMPORARY THERAPEUTIC APPROACHES

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Abstract: Sinus node syndrome (SNS) is a heterogeneous set of disorders that compromise the generation and conduction of electrical impulses by the sinoatrial node, resulting in sinus bradycardia, pauses, chronotropic incompetence, and brady-tachy syndrome. Its pathophysiology involves the interaction between intrinsic mechanisms—such as progressive fibrous degeneration and atrial remodeling—and extrinsic factors, including drugs, metabolic disorders, autonomic dysfunctions, and genetic predisposition. Clinically, it manifests as symptoms of cerebral and systemic hypoperfusion, notably dizziness, syncope, and exercise intolerance. This narrative review analyzed recent evidence on pharmacological therapies, permanent pacemaker indication, and emerging strategies. The data confirm that agents such as theophylline and cilostazol can alleviate symptoms in specific scenarios, but they do not replace pacemakers, which remain the most effective intervention in symptomatic SSS, with a consistent impact on reducing syncope and improving quality of life, although with no proven effect on mortality. New approaches, such as leadless pacemakers, physiological stimulation of the conduction system, and cell/gene therapies, show potential but still lack robust studies, especially in populations with SSS. It is concluded that the management of SSS should be individualized, with exclusion of reversible causes, careful therapeutic evaluation, and use of a pacemaker when indicated. Important gaps remain regarding the role of atrial fibrillation, comorbidities, emerging therapies, and pharmacomodulation of automatism, reinforcing the need for prospective research to improve risk stratification and clinical decision-making.

Keywords: Sinus Node Syndrome; Artificial Pacemaker; Bradycardia; Therapy; Cardiac Electrophysiology; Sinoatrial Node Dysfunction.

INTRODUCTION

Sinus node dysfunction, also known as sinus node syndrome (SNS), represents a spectrum of disorders characterized by the inability of the sinoatrial node (SAN) to generate or conduct electrical impulses properly, resulting in sinus bradycardia, sinus pauses, chronotropic incompetence, or alternation between bradyarrhythmia and tachyarrhythmia (Hawks, Paul & Malu, 2021).

Sinus node syndrome is estimated to affect approximately 0.08% of the population (Elkattawy et al., 2022). This dysfunction can manifest itself in various age groups; however, advanced age is the most relevant risk factor, with a higher prevalence among individuals aged 70 to 89 years. In addition, diseases commonly associated with aging, such as systemic arterial hypertension, diabetes mellitus, chronic kidney disease, and ischemic heart disease, contribute to both the risk and progression of sinus node dysfunction. (Hawks, Paul & Malu, 2021)

The clinical outcome tends to be favorable when appropriate treatment is instituted, since events leading to death are uncommon; in contrast, mortality among individuals without intervention reaches 2%. People affected by SSS often experience increased susceptibility to manifestations of dizziness and syncope. The genesis of these symptoms is connected to the heart's inability to maintain adequate cardiac output due to atrioventricular nodal conduction disorders or the occurrence of paroxysmal supraventricular tachycardias. Although the diagnostic suspicion of the syndrome is often raised by the identification of arrhythmias and arrests, definitive confirmation by Holter electrocardiogram can be a clinical challenge. This is due to the need to differentiate from other clinical conditions that can mimic the findings of SSS. (Elkattawy et al., 2022)

The pathophysiology of SSS involves both intrinsic mechanisms, such as atrial remodeling and progressive fibrous degeneration of the sinoatrial node, and extrinsic factors, including drug use, metabolic disorders, and autonomic dysfunctions (Schmidt et al., 2022; Li et al., 2024). Recent population studies also highlight the role of genetic factors, with variants in genes such as MYH6, KRT8, SCN10A, and TTN/CCDC141 associated with the development of SSS and an increased risk of pacemaker implantation (Thorolfsdottir et al., 2021).

From a clinical standpoint, SSS manifests as persistent sinus bradycardia, sinus pauses or arrests, sinoatrial exit block, and, classically, brady-tachy syndrome — characterized by alternating bradyarrhythmias and supraventricular tachyarrhythmias, especially atrial fibrillation (AF) and atrial flutter (Elkattawy et al., 2022). The relationship between AF and SSS has been widely recognized as bidirectional. Schmidt et al. (2022) demonstrate that AF promotes structural and electrical remodeling of the NSA, contributing to the progressive deterioration of its function, especially after prolonged episodes of tachyarrhythmia. These authors also highlight that patients undergoing radiofrequency ablation for the treatment of

AF may develop SSS through different mechanisms, including pre-existing fibrosis of the NSA, functional atrial remodeling, and iatrogenic effects of the procedure itself.

The clinical presentation results from tissue hypoperfusion caused by bradyarrhythmias, leading to symptoms such as dizziness, presyncope, syncope, exercise intolerance, confusion, and, rarely, seizures due to cerebral hypoperfusion (Hawks, Paul & Malu, 2021; Elkattawy et al., 2022). In specific cases, central nervous system lesions, such as Wallenberg syndrome, can trigger autonomic dysfunction with manifestation of SSS, highlighting the neurocardiogenic influence on NSA modulation (Lee et al., 2021).

Given the functional and prognostic impact, the management of SSS includes the exclusion of reversible causes, the judicious use of drugs, and, in symptomatic cases with documented bradyarrhythmias, the indication for a permanent pacemaker—an intervention that reduces symptoms and improves quality of life, although it does not alter overall mortality (Hawks, Paul & Malu, 2021). In this context, this review aims to synthesize the most recent evidence on therapeutic strategies for SSS, covering pathophysiological and clinical aspects and, especially, pharmacological approaches and the implantation of electrical stimulation devices.

METHODOLOGY

This study is a narrative review of the literature, developed with the aim of critically synthesizing recent evidence related to therapeutic strategies used in the management of SSS. The adoption of this methodological design allowed us to integrate different types of studies and comprehensively contextualize the clinical and pathophysiological advances associated with the condition.

The literature search was performed in the PubMed/MEDLINE database, using the MeSH descriptors "Sick Sinus Syndrome" and "treatment," combined by the Boolean operator AND. In addition, a manual search of the references of the initially selected articles was performed to broaden the scope of the review and minimize possible omission biases.

Articles published in the last five years, available in full in English or Portuguese, that directly addressed therapeutic interventions applied to SSS were included, covering original studies, reviews, clinical trials, guidelines, and case reports. Duplicate publications, studies not directly related to the management of the syndrome, previous narrative reviews, non-indexed articles, and incomplete materials, such as editorials, letters to the editor, and abstracts, were excluded.

The selection of studies took place in two sequential stages: initial screening of titles and abstracts, followed by critical evaluation of eligible full texts. The information extracted was organized descriptively and integrated through narrative synthesis, allowing the identification of trends, advances, and gaps in the contemporary treatment of SSS.

With regard specifically to the use of cilostazol in SSS, no studies published in the last five years were identified. However, the manual search retrieved the works of Sonoura et al. (2019) and Jin et al. (2020), which represent the most recent clinical evidence available on this therapy. Additionally, due

to its normative relevance and the consolidation of international recommendations for the treatment of SSS, the study by Kusumoto et al. (2019) was included, which summarizes the joint ACC/AHA/HRS guidelines (2018), constituting the main current reference for clinical practice.

RESULTS AND DISCUSSION

Pharmacological therapies

In the context of SSS, pharmacological therapy plays an essentially adjuvant and temporary role, being considered an alternative for patients who refuse pacemaker implantation or who cannot undergo the procedure at first. In most cases, the etiology is structural, associated with progressive fibrous degeneration of the NSA, which limits the possibility of drug reversal of the dysfunction. Thus, drugs are used mainly to alleviate symptoms resulting from hypoperfusion associated with bradyarrhythmias and to correct potentially reversible extrinsic factors.

Among the available options, phosphodiesterase inhibitors, such as theophylline and cilostazol, stand out as pharmacological alternatives used in the symptomatic management of SSS. Theophylline may be considered in patients who refuse pacemaker implantation, although its prolonged use is limited by the risk of adverse effects such as nausea, tremors, and arrhythmias (Hawks, Paul & Malu, 2021). Cilostazol, in turn, has demonstrated positive chronotropic effects and good tolerability in retrospective and clinical studies, making it a temporary option in symptomatic patients—findings corroborated by Sonoura et al. (2019) and later confirmed in the comparative study by Jin et al. (2020). (Davi Moreira)

In emergency situations, such as acute symptomatic bradycardia, agents such as atropine, dopamine, epinephrine, or glucagon may be used according to advanced life support protocols, but they are not indicated for chronic use due to the risk of tachyarrhythmias and their systemic adverse effects (Hawks, Paul & Malu, 2021; Kusumoto et al., 2019).

The literature also shows that several drugs used in other clinical settings can precipitate or aggravate SSS. Bradycardic drugs, such as beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, class I and III antiarrhythmics, and lithium, are associated with worsening NSA automaticity. Similarly, experimental studies show that antivirals such as remdesivir can induce significant bradycardia and prolongation of the sinus interval. Li et al. (2024) observed that remdesivir interferes with conduction and automaticity by inhibiting essential ion currents, such as If/HCN4 and IKr/hERG, producing an electrophysiological phenotype compatible with SSS, which reinforces the need for electrocardiographic monitoring in these patients.

Correcting extrinsic causes—such as electrolyte disturbances, hypothyroidism, obstructive sleep apnea, intoxications, and inappropriate use of drugs—is a fundamental step before indicating definitive interventions. In many cases, reversing these factors is sufficient to restore sinus function and avoid pacemaker implantation (Hawks, Paul & Malu, 2021).

The recommendations consolidated by Kusumoto et al. (2019) and other international guidelines reinforce that no phar-

macological agent has efficacy comparable to that of a permanent pacemaker in the treatment of symptomatic SSS. Thus, drug therapy remains a temporary and adjuvant alternative for selected patients who refuse or cannot undergo the procedure immediately, or as a bridge until the definitive device is implanted.

Indication and efficacy of permanent pacemakers

A permanent pacemaker is the main treatment for symptomatic SSS and, to date, is the only intervention capable of effectively and permanently correcting sinoatrial node automatism and conduction disorders. The joint guidelines of the *American College of Cardiology* (ACC), *American Heart Association* (AHA), and *Heart Rhythm Society* (HRS) — ACC/AHA/HRS document (2018), consolidated by Kusumoto et al. (2019)—recommend that the indication for the device be based on the proven correlation between bradyarrhythmias and symptomatic symptoms of tissue hypoperfusion, such as syncope, presyncope, dizziness, fatigue, or exercise intolerance. In this context, marked sinus bradycardia, prolonged sinus pauses, sinoatrial exit block, chronotropic incompetence, and symptomatic brady--tachy syndrome are classic scenarios in which pacemaker implantation is strongly indicated.

From a clinical standpoint, permanent pacemakers have a consistent impact on reducing syncope, presyncope, and functional limitations resulting from bradyarrhythmia, with a significant improvement in quality of life. Classic and contemporary studies confirm that device implantation corrects episodes of prolonged sinus pauses, improves chronotropic incompetence, stabilizes hemodynamics, and reduces hospitalizations related to bradycardia (Hawks, Paul & Malu, 2021; Kusumoto et al., 2019). However, there is no evidence of a reduction in overall mortality in patients with SSS, an aspect reiterated in different reviews and clinical trials.

Even when compared to pharmacological therapies such as cilostazol, the pacemaker remains the most reliable intervention. Although cilostazol can increase heart rate and temporarily delay the need for implantation in some patients, it does not match the device's ability to prevent serious bradyarrhythmic events (Sonoura et al., 2019; Jin et al., 2020). Thus, drugs such as theophylline and cilostazol are considered transitional strategies, indicated mainly for patients who refuse a pacemaker or are waiting for suitable conditions for the procedure.

Thus, permanent pacemakers remain the cornerstone of treatment for symptomatic SSS, backed by consistent evidence and leading international guidelines. Their use should be carefully considered and based on documentation of bradyarrhythmic events, always preceded by investigation and correction of potentially reversible causes.

Emerging approaches

The management of SSS has kept pace with the development of more physiological and less invasive technologies. Although permanent pacemakers remain the treatment of choice in symptomatic cases, according to ACC/AHA/HRS guidelines (Kusumoto et al., 2019), emerging approaches—including leadless pacemakers, physiological pacing, and cell or gene therapies—have sought to reduce device-related complications and, in the future, restore sinus function

through biological or electrophysiological means.

Among the technological innovations, the leadless *pacemaker* stands out, eliminating the need for transvenous electrodes and subcutaneous pockets, avoiding complications typical of conventional systems, such as infection, electrode displacement, and venous thrombosis (Kusumoto et al., 2019). Although its current use is more common in patients with permanent AF, the development of devices with atrial pacing tends to broaden its applicability in SSS.

Another promising approach is physiological *pacing*, such as stimulation of the His bundle and left bundle branch conduction area. These modalities promote more physiological ventricular activation and reduce mechanical dyssynchrony, being particularly relevant in patients with atrial remodeling or increased risk of arrhythmias (Vijayaraman et al., 2021). In parallel, Schmidt et al. (2022) highlight the importance of atrial remodeling in the genesis of AF in patients with SSS. Despite the scarcity of specific studies in this population, recent guidelines already recognize the potential of these techniques as alternatives to right ventricular *pacing* in selected cases (Kusumoto et al., 2019). In this context, current pacing strategies prioritize atrial pacing with minimal ventricular activation, allowing for better adjustment of the chronotropic response—a crucial aspect in chronotropic incompetence and brady-tachy syndrome (Hawks, Paul & Malu, 2021).

Biological pacemakers have gained prominence with advances in the generation of SAN-like cardiomyocytes, obtained through protocols that modulate pathways such as WNT/β-catenin, FGF, and NODAL, allowing the differentiation of pluripotent stem cells into cells with automaticity and high expression of HCN2/HCN4 (Liu et al., 2023; Sleiman et al., 2024). The relevance of these targets is reinforced by genetic studies that associate variants in automatism genes, especially HCN4, with sinus node syndrome (Thorolfsdottir et al., 2021). Despite progress, the clinical application of biological pacemakers still requires proof of safety and electrophysiological stability.

At the same time, recent pharmacological investigations show that antivirals such as remdesivir can directly interfere with ion currents crucial for sinus automaticity (If/HCN4 and IKr/hERG), reproducing a phenotype compatible with SSS (Li et al., 2024). Although initially described as adverse effects, these findings open the door to the development of selective modulators of pacemaker currents, with potential future therapeutic roles.

Together, these emerging approaches reflect a trend toward seeking more physiological, safer, and personalized therapies. Although pacemakers remain the most effective treatment in the current scenario, advances in cellular, ionic, and stimulation technologies point to a future in which sinus automaticity can be restored with less morbidity (Kusumoto et al., 2019; Li et al., 2024).

Prognostic factors (Davi Moreira)

SSS presents heterogeneous evolution, modulated by clinical, structural, and electrophysiological factors that influence its expression and symptomatic recurrence. Population studies demonstrate a strong association with aging, with a higher prevalence of fibrosis and progressive NSA degeneration in elderly individuals, which contribu-

tes to persistent or recurrent manifestations of arrhythmia (Hawks, Paul & Malu, 2021).

The presence of structural atrial disease, especially the coexistence of AF and atrial remodeling, is another relevant prognostic marker. Evidence indicates a bidirectional relationship between AF and SSS: prolonged episodes of tachyarrhythmia promote electrical remodeling and perinodal fibrosis, aggravating sinus dysfunction, while SSS itself favors the onset of AF due to irregularities in atrial automatism (Schmidt et al., 2022). Patients with this combined phenotype tend to have a higher symptom burden, an earlier need for a pacemaker, and worse exercise tolerance.

Cardiovascular and metabolic comorbidities—including hypertension, diabetes mellitus, coronary artery disease, heart failure, and chronic kidney disease—are associated with the development and progression of SSS (Hawks, Paul, & Malu, 2021). These conditions favor structural remodeling and electrophysiological changes in the atrium and the NSA itself. Endocrine disorders, such as hypothyroidism, and electrolyte changes can further aggravate or mimic the condition, reinforcing the need for comprehensive etiological investigation.

Recent pathophysiological evidence, such as the effects of remdesivir on ion currents fundamental to sinus automatism (If/HCN4 and IKr/hERG), indicates that exposure to drugs that interfere with HCN4 and hERG channels may precipitate or aggravate SSS in predisposed patients (Li et al., 2024), constituting an important clinical warning sign and justifying closer cardiological surveillance.

Regarding therapeutic response, Sonoura et al. (2019) observed that the use of cilostazol was associated with a temporary reduction in the need for pacemakers in symptomatic patients, suggesting a less aggressive clinical course in the short term in responders. However, this benefit does not change the natural history of SSS, and pacemakers remain the definitive intervention in most cases.

In general, greater symptomatic burden, structural or electrical comorbidities, presence of AF, advanced atrial remodeling, and recurrent episodes of syncope are associated with a less favorable outcome and the need for earlier intervention. The ACC/AHA/HRS guidelines (Kusumoto et al., 2019) emphasize that prognosis depends fundamentally on the correlation between bradyarrhythmias and symptoms, with persistent cerebral hypoperfusion being one of the main determinants for pacemaker indication and subsequent improvement in quality of life.

Current evidence and controversies

Despite advances in understanding SSS, key aspects of its pathophysiology remain under discussion. Although progressive fibrous degeneration of the sinus node is the most widely accepted intrinsic mechanism, the relative impact of extrinsic factors on its genesis and progression remains controversial. Recent evidence shows that drugs such as beta-blockers, calcium channel blockers, antiarrhythmics, and certain antivirals can precipitate or aggravate sinus dysfunction (Hawks, Paul & Malu, 2021; Li et al., 2024), making it difficult to distinguish between primary SSS and manifestations secondary to drug use.

The bidirectional relationship between SSS and AF is another central point of controversy. Although there is robust evidence that prolonged episodes of AF promote atrial remodeling and worsening sinus dysfunction (Schmidt et al., 2022), it remains debated whether AF should be interpreted predominantly as a cause, consequence, or both in the deterioration of NSA.

In the therapeutic setting, contemporary guidelines recognize that pacemakers consistently improve SSS symptoms but have no clear effect on mortality or hard outcomes (Kusumoto et al., 2019), which motivates interest in complementary strategies capable of modifying the course of the disease. In this scenario, prolonged use of agents such as theophylline and cilostazol has shown promise in specific subgroups, but their application remains limited by the absence of robust randomized trials and the non-negligible risk of arrhythmias (Sonoura et al., 2019).

Although emerging technologies in cardiac pacing are evolving, their application in SSS remains limited by the absence of specific trials and the pathophysiological complexity demonstrated in genetic and pharmacological studies (Thorolfsdottir et al., 2021; Li et al., 2024).

Finally, experimental findings involving drugs such as remdesivir, capable of interfering with If/HCN4 and IKr/hERG currents, reignite discussions about electrophysiological vulnerability and the impact of contemporary therapies on the cardiac conduction system (Li et al., 2024).

In summary, although current knowledge about SSS is substantially more robust than in previous decades, there are still significant gaps. The interface between intrinsic and extrinsic factors, the exact role of AF, the magnitude of the benefit of pacemakers, and the place of emerging therapies remain under development, constituting priority areas for research and refinement of guidelines.

It should be noted that, due to normal age-related physiological changes in the heart's conduction system, such as fibrosis and sclerosis, sinus node syndrome is common in the elderly. Although some patients are asymptomatic, the following signs and symptoms are common: arrhythmias, dizziness, vertigo, confusion, and syncope. A rare but serious clinical manifestation is seizures, which can be tonic or clonic and develop when the decrease in cardiac output is prolonged, leading to an extended period of cerebral hypoperfusion (Elkattawy et al., 2022).

This last manifestation is concerning because, if the diagnosis is not made correctly, anticonvulsant drugs are administered, and because they are proarrhythmic drugs, they can aggravate the condition and increase the risk of sudden cardiac death. Therefore, in an emergency, it is essential that the medical team be vigilant and perform a cardiac assessment of patients with seizures, especially if they are elderly and have no history of previous seizures (Elkattawy et al., 2022).

The definitive diagnosis of sinus node dysfunction is established when symptoms of hypoperfusion, such as syncope or presyncope, are directly correlated with documented bradyarrhythmia ( ) (Kendall et al., 2021). Identifying reversible extrinsic causes, such as the use of certain medications, is a key step before defining long-term therapy (Kendall et al., 2021).

Several drugs can induce or exacerbate SSS. One example is propranolol, a beta-blocker known to cause bradycardia (Elkattawy et al., 2022). Recently, the antiviral Remdesivir (RDV) has also been associated with adverse cardiac events. Experimental studies have shown that RDV can induce sinus bradycardia, conduction block, and sinus arrest, mimicking the symptoms of SSS (Li et al., 2024). The underlying mechanism appears to involve significant inhibition of the I_f current in HCN4 channels, crucial for sinus node automatism, and the I_{Kr} current in hERG channels (Li et al., 2024).

For patients with confirmed symptomatic SSS, where extrinsic causes have been ruled out or cannot be reversed, the first-line treatment is permanent pacemaker implantation (Kendall et al., 2021). The main goal of this intervention is symptom relief and improved quality of life (Kendall et al., 2021). In cases of severe bradycardia or syncope, pacemakers have been shown to be highly effective in resolving symptoms, as observed in case reports where device implantation led to complete resolution of syncopal episodes and even associated seizures (Elkattawy et al., 2022; Hayashi et al., 2023).

The preferred pacing strategy is atrial, with minimal ventricular pacing, as right ventricular pacing has been shown to be associated with an increased risk of arrhythmias and decreased cardiac function (Kendall et al., 2021). In patients who refuse a pacemaker, or in cases where the indication is not absolute, phosphodiesterase inhibitors (such as theophylline or cilostazol) may be considered as a secondary option for symptomatic control (Kendall et al., 2021). In addition, in patients who have self-limiting episodes and become asymptomatic, as in some cases after a spinal cord stroke, clinical observation without invasive intervention may be an appropriate course of action, provided it is monitored (Lee et al., 2021).

Although there are medication options, the response to pharmacological treatment of SSS offers limited and inconclusive benefits for patients with the syndrome. In addition, the use of phosphodiesterase inhibitors can cause adverse effects such as tremors, headaches, and palpitations, and requires close monitoring to avoid toxic doses during use.

Thus, the most recent guidelines and reviews suggest that such drugs should only be considered in selected cases and under strict clinical monitoring (Kendall et al., 2021; Barnes, 2010).

CONCLUSION

SSS is a heterogeneous and multifactorial condition, whose clinical expression results from the interaction between intrinsic degeneration of the sinoatrial node and a variety of extrinsic factors capable of modulating or aggravating its function. The evidence gathered demonstrates that, although pharmacological therapies may offer symptomatic relief in specific contexts, no has efficacy comparable to permanent pacemakers as a definitive intervention for symptomatic patients. Thus, device implantation remains the therapeutic mainstay, promoting significant improvement in symptoms and quality of life, although without a proven impact on mortality.

Emerging technologies—including leadless pacemakers, physiological pacing

strategies, and investigational cell therapies—offer promising prospects, but robust and specific evidence for SSS is still lacking. At the same time, the effect of modern drugs, such as antivirals capable of interfering with ion currents essential to cardiac automatism, reinforces the need to broaden our understanding of electrophysiological vulnerability and therapeutic safety.

Given this scenario, there is a clear need for prospective studies to elucidate the role of comorbidities, atrial remodeling, emerging therapies, and pharmacological modulators in the progression of the disease. Advances in knowledge in these areas may enable more physiological, personalized strategies that could potentially modify the natural history of SSS. In this sense, an integrated understanding of pathophysiological mechanisms, available therapeutic approaches, and current controversies is essential to improve clinical practice and guide the development of new guidelines and interventions.

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