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Does Hypothyroidism Influence Left Bundle Branch Area Pacing Outcomes? Mechanistic Insights and Clinical Implications

Ashwin Shajith[1]; Aparna Salimon[1]

[1]6th Year Undergraduate Student Tbilisi State Medical University Tbilisi, Georgia

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Abstract: Left bundle branch area pacing (LBBAP) has become the dominant modality for physiological cardiac pacing, offering near-physiological ventricular activation with low and stable capture thresholds. Despite its widespread adoption, patient-specific factors that may impair LBBAP threshold stability, left bundle branch (LBB) capture reliability, and long-term functional outcomes remain incompletely defined. Hypothyroidism is the most prevalent endocrine disorder in South Asia, affecting approximately 11% of Indian adults — two to three times the prevalence reported from Western populations. A 2025 retrospective study of 31,774 consecutive pacemaker recipients found that 12.9% had thyroid dysfunction at implantation, with TSH testing performed in fewer than 53% before the procedure. Hypothyroidism exerts well-characterised effects on myocardial calcium cycling, ion channel kinetics, connexin-43 (Cx43) gap junction expression, and interstitial fibrosis — each mechanistically relevant to conduction system capture and threshold stability in LBBAP. To our knowledge, no published study has specifically examined hypothyroidism as a modifier of LBBAP outcomes. This review synthesises published evidence to propose and support a clinical hypothesis: that hypothyroidism may adversely influence LBBAP by raising pacing thresholds, impairing reliable LBB engagement, widening paced QRS duration, and increasing susceptibility to pacing-induced cardiomyopathy (PICM) — through thyroid hormone-dependent alterations in SERCA2a-mediated calcium cycling, SCN5A and HCN4 expression, Cx43 localisation, and TGF-β1-driven septal fibrosis. Direct clinical validation is absent, and prospective studies are required. Routine pre-procedural thyroid function screening before elective LBBAP may represent a clinically actionable, low-cost intervention warranting formal evaluation, particularly in South Asian electrophysiology centres.

Keywords: *Left Bundle Branch Area Pacing; Hypothyroidism; Conduction System Pacing; Pacing Threshold; Pacing-Induced Cardiomyopathy; Thyroid Dysfunction.*

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I. INTRODUCTION

Left bundle branch area pacing (LBBAP) has rapidly become the dominant strategy for physiological cardiac pacing since its introduction by Huang et al. in 2017 [1]. By targeting the subendocardial interventricular septum (IVS) to capture left bundle branch (LBB) fibres or their fascicular extensions, LBBAP produces near-physiological left ventricular (LV) activation with narrow paced QRS durations and stable capture thresholds [2]. The multicentre European MELOS registry (n = 2,533) demonstrated overall LBBAP success rates of 92.4% for bradyarrhythmia indications [3], and the 2024 International Tendril Registry confirmed acute and 6-month threshold stability at 0.8 ± 0.3 V at 0.4 ms across 221 patients at 11 international sites [4]. The 2023 HRS/APHRS/LAHRS Guideline on Cardiac Physiologic Pacing and the 2025 ESC/EHRA Clinical Consensus Statement on Conduction System Pacing both provide Class IIa or equivalent recommendations for LBBAP, endorsing it as the primary conduction system pacing (CSP) strategy [5], [6].

Despite these advances, patient-specific factors that may adversely influence LBBAP threshold stability and LBB capture reliability are incompletely characterised. No existing LBBAP registry or guideline specifically addresses the influence of thyroid function on pacing outcomes. This gap is clinically significant: hypothyroidism is not only a recognised reversible cause of bradyarrhythmias [7] but also a systemic metabolic disorder that imposes multiple relevant changes on myocardial electrophysiology, calcium handling, gap junction expression, and interstitial fibrosis — all factors mechanistically linked to pacing threshold and conduction system capture.

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Hypothyroidism carries a disproportionately high prevalence in South Asia. A nationwide Indian study across eight cities found an overall adult hypothyroidism prevalence of 10.95%, significantly exceeding the 2–4.6% figures reported from Western cohorts [8], [9]. A 2024 cross-sectional study from a New Delhi tertiary centre confirmed that autoimmune thyroid disease now accounts for 78.8% of hypothyroid cases in India, reflecting a post-iodisation shift from iodine deficiency to Hashimoto's thyroiditis — a pattern associated with a higher rate of progression to overt hypothyroidism than observed in Western populations [9]. Crucially, a 2025 retrospective analysis of 31,774 consecutive pacemaker recipients from a national database found that 12.2% had subclinical and 0.7% had overt hypothyroidism at implantation, with TSH testing performed in fewer than 53% of patients in the 6 months before implant [10]. To our knowledge, no published study has specifically examined thyroid dysfunction in the context of LBBAP, representing a directly addressable research gap of particular relevance to Indian and South Asian electrophysiology centres.

This review synthesises current evidence on the electrophysiological and structural cardiac consequences of hypothyroidism, examines their potential relevance to LBBAP performance, and proposes a clinical hypothesis with a structured research framework for prospective investigation.

II. OBJECTIVES

The primary objective of this review is to examine whether hypothyroidism can plausibly influence left bundle branch area pacing outcomes and to propose a mechanistic hypothesis linking thyroid dysfunction to pacing threshold instability, impaired LBB capture, and pacing-induced cardiomyopathy.

This review aims to summarise the procedural, anatomical, and substrate determinants of LBBAP success; describe the electrophysiological and structural cardiac effects of hypothyroidism relevant to conduction system capture; evaluate indirect and analogical clinical evidence linking thyroid status with pacing performance; and outline the clinical implications and a prospective research framework capable of testing the proposed hypothesis. By integrating evidence from cardiac electrophysiology and endocrinology, this review seeks to highlight thyroid dysfunction as a potentially modifiable, under-recognised determinant of LBBAP performance, particularly in South Asian populations where hypothyroidism prevalence is disproportionately high.

III. METHODOLOGY

This narrative review was conducted to evaluate the relationship between hypothyroidism and left bundle branch area pacing outcomes, with particular focus on pacing threshold stability, LBB capture reliability, and pacing-induced cardiomyopathy risk. Relevant literature was identified through searches of major biomedical databases including PubMed, Scopus, and Google Scholar. Keywords used included left bundle branch area pacing, conduction system pacing, pacing threshold, hypothyroidism, thyroid dysfunction, pacing-induced cardiomyopathy, and thyroid cardiac electrophysiology. Priority was given to large multicentre pacing registries, guideline statements, mechanistic and molecular studies of thyroid hormone action on the myocardium, and clinical studies addressing thyroid dysfunction in pacemaker populations. Reference lists of selected articles were also screened to identify additional relevant studies. Because no published study has directly examined hypothyroidism in the context of LBBAP, this review necessarily draws on indirect and analogical evidence from conventional pacing, thyroid cardiac electrophysiology, and pacing-induced cardiomyopathy literature to construct a hypothesis-generating synthesis.

IV. DETERMINANTS OF LBBAP SUCCESS AND THRESHOLD STABILITY

- *Procedural, Anatomical, and Substrate Factors*

LBBAP success is primarily determined by operator experience, anatomical septal geometry, and lead depth. The MELOS registry demonstrated that the procedural learning curve plateaus at approximately 250 cases [3]. Confirmed LBB capture — evidenced by an LBB potential, stimulus-to-left ventricular activation time (LVAT) < 80 ms, and a V1 r' morphology during non-selective capture — is achieved in approximately 70–85% of successful implants; the remainder achieve left ventricular septal pacing (LVSP) without electrophysiological confirmation of LBB engagement [4].

The local myocardial substrate at the lead–tissue interface is an increasingly recognised determinant of chronic threshold behaviour. Local fibrosis surrounding a pacing lead is a documented cause of late threshold rise and loss of capture in conduction system pacing, confirmed on cardiac MRI T1 mapping [11]. Myocardial infiltration (amyloidosis, sarcoidosis) and metabolic disorders including diabetes and uraemia are established risk factors for permanent threshold rise in conventional pacing [12]. In heart failure patients, LBBAP success rates fell to 82.2% versus 92.4% in bradyarrhythmia patients in the MELOS registry, attributed to IVS fibrosis and myopathic changes in the LBB network substrate [3].

- *The Threshold Concept in LBBAP: Beyond Myocardial Excitability*

Pacing threshold in LBBAP is not simply a function of electrode-to-myocardium contact. It represents the minimum energy required to depolarise the LBB network from a specific anatomical position through a tissue matrix whose electrical properties are determined by local cardiomyocyte excitability, intercellular coupling efficiency, extracellular matrix composition, and the electrolyte milieu. Standard pacing references list hypothyroidism as a metabolic cause of threshold elevation in conventional pacing [12], but its specific influence on LBBAP has not been studied. The critical distinction in LBBAP is that any process disrupting electrical coupling between electrode and LBB fibres — through fibrosis, ion channel downregulation, or impaired

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gap junction function — may selectively impair conduction system capture even when lower-output myocardial capture is preserved. This represents a functional downgrade from physiological to non-physiological pacing and may expose patients to PICM risk.

V. CARDIAC ELECTROPHYSIOLOGICAL AND STRUCTURAL EFFECTS OF HYPOTHYROIDISM

➢ *Thyroid Hormone as a Master Cardiac Gene Regulator*

Triiodothyronine (T3) regulates a broad suite of cardiac genes governing both mechanical and electrical function [13]. Positively regulated targets include SERCA2a (sarcoplasmic reticulum Ca^{2+}-ATPase 2a), α-myosin heavy chain, HCN4, and Na^{+}/K^{+}-ATPase; negatively regulated targets include β-myosin heavy chain, phospholamban (PLN), and sarcolipin (SLN) — both of which tonically inhibit SERCA2a [13], [14]. RNA-seq studies in human iPSC-derived cardiomyocytes have confirmed T3-mediated regulation of multiple cardiac repolarisation genes including ATP2A2, HCN4, and CACNB2, underlining the breadth of T3's influence on cardiomyocyte electrical behaviour [14]. In hypothyroidism, SERCA2a expression falls while PLN and SLN rise, impairing sarcoplasmic reticulum calcium reuptake, prolonging the calcium transient, and slowing myocardial relaxation. These changes elevate the energy requirement for membrane depolarisation and are expected to raise the threshold for electrical capture.

➢ *Ion Channel Remodelling, Conduction Slowing, and Acquired Long QT*

Hypothyroidism produces a well-characterised cardiac electrical phenotype: sinus bradycardia, prolonged PR interval, widened QRS, and QTc prolongation with increased QT dispersion [15]. The ionic basis includes downregulation of SCN5A (encoding Nav1.5), which reduces the rate of action potential upstroke (max dV/dt) and slows conduction velocity through both working ventricular myocardium and the His–Purkinje system [15]. Reduced HCN4 expression diminishes the pacemaker current (If), contributing to sinus node dysfunction and slowed AV conduction — explaining why hypothyroidism is a recognised reversible cause of AV block and sinus node dysfunction [7], [15]. A landmark study by Capraro et al. (2024) demonstrated that TSH itself — independently of T3 deficiency — directly reduces repolarising K^{+} currents, suggesting a dual mechanism for electrical remodelling in primary hypothyroidism: T3 deficiency-mediated transcriptional effects compounded by direct TSH-mediated ion channel suppression [15]. Hypothyroidism is listed as an established cause of acquired long QT syndrome in the 2024 Heart Rhythm O2 comprehensive LQTS review [16]. In LBBAP specifically, conduction slowing in a hypothyroid septum may widen the paced QRS even when the lead is anatomically correctly positioned, because the speed of LBB network propagation governs paced QRS width.

➢ *Connexin-43 Remodelling and Intercellular Coupling*

Connexin-43 (Cx43), the principal gap junction protein in ventricular myocardium, is localised at the intercalated disc and facilitates rapid cell-to-cell electrical propagation [17]. In hypothyroid animal models, Cx43 phosphorylation at Ser368 is altered and its spatial distribution shifts from intercalated disc towards lateral membrane — a pattern that impairs directional propagation, increases anisotropic conduction, and reduces coupling efficiency [18]. Chronic Cx43 remodelling also promotes myofibroblast activation and interstitial collagen deposition through TGF-β signalling, further compounding conduction impairment [17]. These mechanisms may collectively raise the stimulus energy required to recruit LBB fibres during LBBAP, and are relevant given growing evidence that Cx43 distribution is a determinant of pacing threshold in conduction system pacing.

➢ *TGF-β1-Mediated Fibrosis and Septal Structural Changes*

Hypothyroidism is profibrotic. The Guerra et al. study in a validated rat model of induced hypothyroidism demonstrated significantly elevated TGF-β1, TNF-α, IL-6, cardiac troponin T, and BNP, alongside histopathological confirmation of interstitial fibrosis and left ventricular chamber dilatation [13]. Human evidence is provided by native myocardial T1 mapping with cardiac MRI: Patel et al. demonstrated significantly elevated septal T1 values in hypothyroid patients compared with euthyroid controls, indicative of diffuse interstitial expansion consistent with collagen deposition, partially normalising after six months of levothyroxine therapy [19]. As the IVS is the precise anatomical target of LBBAP, elevated septal T1 — signifying greater interstitial fibrosis — translates mechanistically into higher electrical impedance at the pacing site, greater physical resistance to lead helix advancement, and reduced electrical coupling between electrode and LBB fibres. These mechanisms require prospective clinical confirmation in the specific context of LBBAP.

Notably, the Guerra et al. study also observed that rapid thyroid hormone repletion initially increased inflammatory and fibrotic markers and induced myocardial cellular infiltration before producing net benefit [13], suggesting that a gradual, controlled approach to thyroid normalisation before elective LBBAP may be preferable to rapid T3 repletion.

VI. CLINICAL EVIDENCE LINKING THYROID FUNCTION AND PACING OUTCOMES

Direct clinical evidence for a thyroid–LBBAP interaction is absent. The following lines of indirect and analogical evidence collectively support the biological plausibility of the proposed hypothesis; none individually is definitive, and prospective confirmation is required before clinical recommendations can be formalised.

Hypothyroidism is a recognised, albeit uncommon, reversible cause of AV block and sinus node dysfunction [7]. A retrospective analysis by Sisti et al. found that thyroid hormone replacement produced partial or complete recovery of AV conduction in a subset of patients, though most required permanent pacing regardless [7]. When residual hypothyroidism persists at LBBAP implantation, subsequent

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thyroid normalisation with levothyroxine may alter the pacing substrate, potentially introducing instability in threshold and capture characteristics during the critical early post-implant period.

The 2025 Avidan et al. analysis of 31,774 consecutive pacemaker recipients found TSH testing in only 52.7% of patients within 6 months before implantation; 12.2% had subclinical and 0.7% had overt hypothyroidism [10]. Patients with thyroid dysfunction were predominantly female, older, and had higher comorbidity burden — a demographic profile closely matching the contemporary LBBAP population. The authors explicitly called for further research into the role of thyroid status in conduction abnormality reversibility [10].

A published case report by Bharati et al. described atrial pacing lead dysfunction — manifesting as threshold rise and undersensing — as a direct clinical consequence of hypothyroidism, normalising following levothyroxine therapy without lead revision [20]. This case provides direct clinical proof-of-concept that hypothyroid myocardial changes are sufficient to produce clinically meaningful lead performance deterioration that is at least partially reversible.

Diabetes mellitus has been established as an independent predictor of permanent RV pacing threshold rise through oxidative stress-mediated myocardial fibrosis [12]. This confirms the principle that systemic metabolic disease can impair chronic pacing performance through fibrotic mechanisms directly analogous to those proposed here for hypothyroidism.

VII. PACING-INDUCED CARDIOMYOPATHY AND THE HYPOTHYROID COMPOUNDING EFFECT

Pacing-induced cardiomyopathy (PICM) is defined as a ≥10% absolute decline in left ventricular ejection fraction (LVEF) to ≤50%, in patients with high ventricular pacing burden and no other identifiable cause [21]. It develops in 10–20% of patients undergoing chronic right ventricular pacing (RVP) over 2–4 years [21]. Independent predictors include reduced baseline LVEF (<55%), wider paced QRS duration (>160 ms), and higher RV pacing burden (>33%); paced QRS duration is the key modifiable risk factor [22].

LBBAP mitigates PICM risk through near-physiological ventricular activation. A systematic review and meta-analysis of 16 studies confirmed that LBBAP consistently improves LVEF and reduces QRS duration compared with conventional pacing [23], and a 2025 meta-analysis of 24 studies and 6,538 patients confirmed significantly lower PICM risk with LBBAP versus biventricular pacing [24]. Despite this, PICM under LBBAP is not eliminated — particularly when confirmed LBB capture is not achieved and LVSP is the actual pacing mode, or when LBB capture is lost during follow-up.

The hypothyroid cardiomyopathy that develops independently of pacing represents a compounding risk for PICM in LBBAP recipients. If hypothyroid patients more frequently achieve LVSP rather than confirmed LBB capture (due to impaired septal coupling), and if their paced QRS is consequently wider (due to slowed conduction velocity), then the two most powerful PICM predictors — paced QRS duration and pacing burden — would both be worsened by the hypothyroid substrate. A pre-existing reduction in LVEF from hypothyroid cardiomyopathy would further amplify baseline PICM risk. This three-way interaction between hypothyroid cardiomyopathy, degraded LBBAP capture quality, and wider paced QRS is biologically plausible but has not been studied; it forms a core motivation for the research framework proposed in Section X.

VIII. THE HYPOTHYROIDISM–LBBAP HYPOTHESIS

Based on the evidence reviewed, we hypothesise that hypothyroidism may adversely influence LBBAP through the following mechanistic cascade:

Hypothyroidism → [SERCA2a↓, Cx43 redistribution, SCN5A↓, TGF-β1↑ fibrosis] → impaired LBB network recruitment + elevated septal impedance → higher pacing threshold + wider paced QRS + reduced confirmed LBB capture rate → increased PICM susceptibility in patients with high ventricular pacing burden.

This proposed pathway is summarised in Fig. 1. Each mechanistic step is supported by published molecular and electrophysiological data as reviewed in Section V; however, the composite effect on LBBAP-specific outcomes has not been directly measured and requires prospective clinical validation. Table 1 provides a structured overview linking molecular targets, hypothyroid changes, electrophysiological consequences, and predicted LBBAP impacts.

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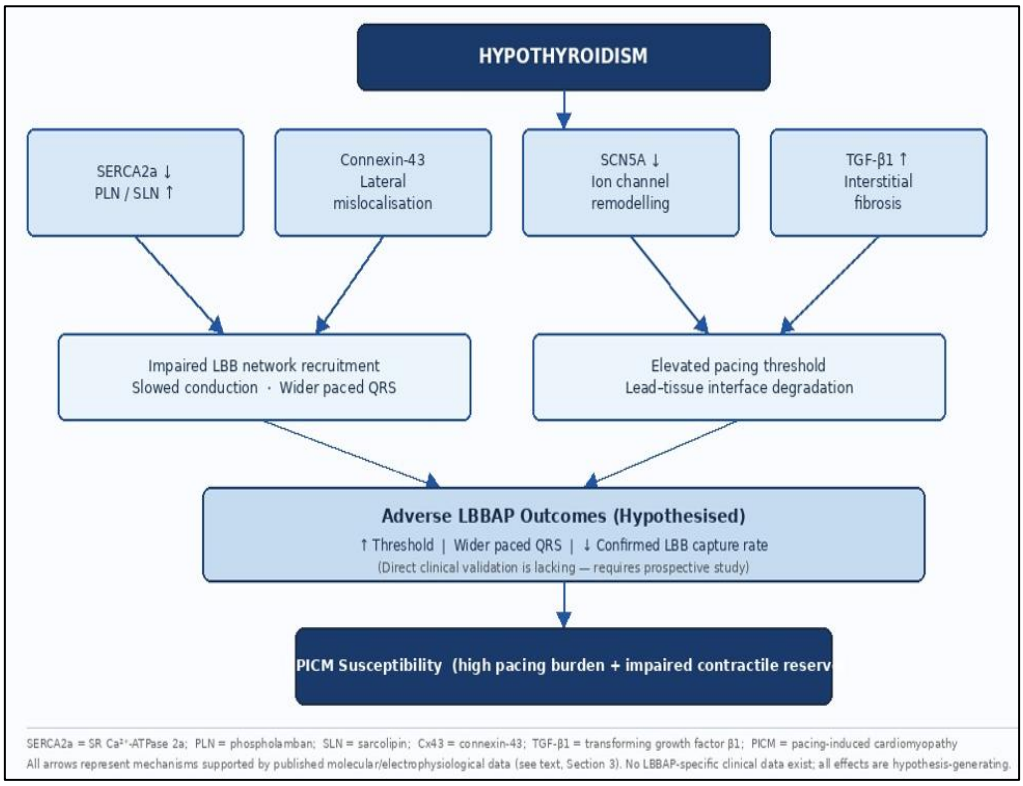

Fig 1 Proposed Mechanistic Pathway Linking Hypothyroidism to Adverse LBBAP Outcomes.

Each arrow represents a mechanism supported by published evidence (see Section V). Direct clinical validation in LBBAP patients is absent; all depicted effects are hypothesis-generating. SERCA2a = sarcoplasmic reticulum Ca^{2+}-ATPase 2a; PLN = phospholamban; SLN = sarcolipin; Cx43 = connexin-43; PICM = pacing-induced cardiomyopathy; LBB = left bundle branch.

Table 1 Proposed Mechanistic Links between Hypothyroidism and LBBAP Outcome Domains

Molecular target	Hypothyroid change	Electrophysiological consequence	Hypothesised LBBAP impact
SERCA2a / PLN / SLN	SERCA2a downregulation; PLN/SLN upregulation	Impaired SR Ca^{2+} reuptake; prolonged AP duration; raised excitability threshold	Raised acute and chronic capture threshold
SCN5A (Nav1.5)	Downregulation	Reduced AP upstroke velocity; slowed His–Purkinje conduction	Wider paced QRS even with correct lead position; ↑ PICM risk
HCN4 (If)	Downregulation	Sinus bradycardia; slowed AV conduction	Higher ventricular pacing burden → greater cumulative PICM exposure
KCNQ1 / IKs	Reduced IKs current	Prolonged repolarisation; acquired long QT substrate	Threshold instability; compounded arrhythmic risk
Connexin-43	Lateral mislocalisation; altered Ser368 phosphorylation	Slowed, anisotropic conduction; impaired cell-to-cell coupling	Reduced LBB network recruitment efficiency; wider paced QRS
TGF-β1 / Collagen	Upregulation; interstitial fibrosis; ↑ ECM deposition	Elevated tissue impedance; diffuse IVS interstitial expansion	Higher threshold; accelerated chronic threshold rise

All mechanistic links are derived from published molecular and electrophysiological data cited in the text. Direct clinical confirmation in LBBAP patients is absent and required before these interactions can be considered established. AP = action potential; SR = sarcoplasmic reticulum; PLN = phospholamban; SLN = sarcolipin; ECM = extracellular matrix; IVS = interventricular septum; PICM = pacing-induced cardiomyopathy; LBB = left bundle branch.

IX. CLINICAL IMPLICATIONS

➢ *Pre-Procedural Thyroid Function Screening*

Neither the 2023 HRS/APHRS/LAHRS Guideline nor the 2025 ESC/EHRA Clinical Consensus Statement specifically mandates thyroid function assessment in the pre-LBBAP workup [5], [6]. The 2025 Avidan et al. data demonstrate that thyroid dysfunction is prevalent in the pacemaker population and significantly under-screened [10]. We propose that TSH and free T4 measurement should be incorporated into the standard pre-LBBAP workup as a simple, low-cost investigation with the potential to identify a

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modifiable substrate abnormality. This is particularly relevant in South Asian centres where background hypothyroidism prevalence is two to three times higher than in Western practice [8], [9]. Formalising this recommendation requires prospective evidence that thyroid status measurably influences LBBAP outcomes.

➢ *Thyroid Optimisation before Elective Implantation*

For patients with overt hypothyroidism undergoing elective LBBAP, deferring the procedure until TSH normalises with levothyroxine replacement (target TSH 0.5–2.5 mIU/L) may be reasonable where urgency permits. This mirrors the established principle of pre-procedural optimisation of reversible metabolic contributors before device therapy. A gradual titration over 6–8 weeks, rather than rapid repletion, may be preferable given the transient pro-inflammatory phase observed during rapid thyroid normalisation [13]. For subclinical hypothyroidism, treatment should be individualised based on TSH level, anti-TPO antibody status, and symptoms. For urgent LBBAP in an overtly hypothyroid patient, clinicians should anticipate potentially higher thresholds, programme with a generous output safety margin, and plan early post-operative thyroid optimisation and threshold reassessment at 3 and 6 months.

➢ *Post-Implantation Monitoring*

If prospective data confirm the hypothesis, LBBAP recipients with known hypothyroidism may benefit from: (1) pacing clinic review at 1 and 3 months rather than the standard 1 and 12 months; (2) threshold reassessment at thyroid function follow-up visits; (3) echocardiographic LVEF assessment at 6 months rather than 12 months in those with pacing burden exceeding 40%; and (4) vigilance for QRS widening on device interrogation as a potential indicator of loss of LBB capture in the context of deteriorating thyroid control. These are hypothesis-contingent recommendations requiring validation before incorporation into routine protocols.

X. PROPOSED RESEARCH FRAMEWORK

To test the hypothesis advanced in this review, a prospective observational cohort study is proposed at two to four South Asian EP centres with established LBBAP programmes and co-located endocrinology services. The study must be prospectively registered with the Clinical Trials Registry of India (CTRI) before the first patient enrolment, and Institutional Ethics Committee (IEC) approval obtained per site, in compliance with ICMJE requirements and the Declaration of Helsinki.

Adults (≥18 years) undergoing LBBAP for any standard indication should be enrolled consecutively and stratified by pre-procedural TSH and free T4 into three groups: euthyroid (TSH 0.4–4.5 mIU/L), subclinical hypothyroid (TSH 4.5–10.0 mIU/L, normal fT4), and overt hypothyroid (TSH >10.0 mIU/L, low fT4). The primary endpoint should be LBBAP pacing threshold at 12 months. Secondary endpoints should include confirmed LBB capture rate, paced QRS duration, LVEF change, and PICM incidence (defined as ≥10% absolute LVEF decline to ≤40% with ≥40% VP burden and no other identified aetiology) [21].

A formal sample size calculation based on published intra-cohort threshold variability (±0.3 V) [4] estimates that approximately 80 patients per group (n = 240 total) would provide 80% power to detect a 0.3 V between-group difference at two-sided $\alpha = 0.05$, after 15% attrition correction. Multivariable linear regression should test TSH as a continuous predictor of 12-month threshold, adjusting for age, sex, diabetes, baseline LVEF, lead type, and pacing burden. A pre-specified subgroup analysis of overt hypothyroid patients achieving versus not achieving TSH normalisation by 6 months would provide the most direct evidence for or against a causal relationship. Table 2 summarises the proposed design.

Table 2 Proposed Design Elements for the Prospective LBBAP–Hypothyroidism Cohort Study

Element	Proposed specification	Rationale
Study design	Prospective multicentre observational cohort	Standardised thyroid classification; avoids retrospective data gaps
Setting	2–4 South Asian EP centres with ≥50 LBBAP/year	High background hypothyroidism prevalence; high LBBAP volumes; epidemiologically relevant
Thyroid groups	Euthyroid / Subclinical HT / Overt HT	Enables dose-response analysis by TSH severity; anti-TPO for autoimmunity stratification
Primary endpoint	Pacing threshold at 12 months	Objective, standardised, actionable LBBAP metric with published intra-cohort variability
Sample size	~80/group (n=240 total)	80% power; α=0.05; 0.3V between-group difference; 15% attrition buffer
Follow-up	12 months (visits at 1, 3, 6, 12 months)	Captures both early and medium-term threshold dynamics and PICM risk window
Registration / Ethics	CTRI (prospective); IEC per site; written consent	ICMJE / journal submission requirement; Declaration of Helsinki compliance

HT = hypothyroid; EP = electrophysiology; CTRI = Clinical Trials Registry of India; IEC = Institutional Ethics Committee; LBBAP = left bundle branch area pacing.

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XI. LIMITATIONS

This review presents a mechanistic hypothesis derived from indirect and analogical evidence. Several specific limitations must be acknowledged transparently.

First, the molecular mechanisms described (SERCA2a, Cx43, SCN5A, TGF-β1) are predominantly characterised in animal models or in vitro systems. Their precise magnitude in the human hypothyroid IVS and their quantitative contribution to LBBAP capture threshold are unknown. Extrapolation to clinical LBBAP outcomes must be treated with caution.

Second, the distinction between conduction system capture (LBB fibre recruitment) and myocardial capture in LBBAP is qualitatively different from the threshold mechanism in conventional RVP. Whether hypothyroid-induced changes differentially affect LBB fibre capture versus myocardial capture has not been studied.

Third, the cardiac effects of subclinical hypothyroidism are heterogeneous and less consistently demonstrated than for overt disease. Whether subclinical TSH elevation produces sufficient substrate changes to measurably influence LBBAP performance is genuinely uncertain, and subclinical hypothyroidism should be regarded as a secondary rather than primary investigative focus in the proposed study.

Fourth, South Asian thyroid epidemiology is regionally heterogeneous [8], [9]. Institutional hypothyroid prevalence at any LBBAP centre may differ substantially from national estimates, and enrolment site selection will influence the study's generalisability.

Fifth, the rapid thyroid normalisation caveat from the Guerra et al. data introduces a complexity: the optimal thyroid treatment strategy before elective LBBAP (pace of titration, target TSH range, timing relative to implant) requires dedicated investigation that goes beyond the scope of the hypothesis presented here.

XII. FUTURE RESEARCH DIRECTIONS

Despite the biological plausibility outlined in this review, several important questions remain unresolved. Future research should prioritise the prospective observational cohort study proposed in Section X to establish whether pre-procedural TSH independently predicts LBBAP pacing threshold, confirmed LBB capture rate, and paced QRS duration.

Further investigations are also needed to determine whether thyroid hormone replacement before elective LBBAP measurably improves capture threshold and LBB engagement, and to define the optimal pace and target of thyroid normalisation given the transient pro-inflammatory phase observed with rapid repletion [13].

Mechanistic studies correlating pre-implant thyroid status with septal tissue characterisation — for example native T1 mapping at the planned LBBAP implant site — may help establish a direct structural link between hypothyroid fibrosis and pacing threshold in humans, bridging the current animal-to-human evidence gap [19].

Finally, longer-term studies are needed to determine whether hypothyroid LBBAP recipients experience higher rates of PICM and loss of LBB capture during follow-up, and whether structured thyroid monitoring after implantation reduces this risk. Multicentre South Asian registries with systematic thyroid function documentation would substantially strengthen the evidence base.

XIII. CONCLUSION

Hypothyroidism is prevalent in South Asian pacemaker populations, frequently under-evaluated before implantation [10], and mechanistically capable of adversely influencing each key determinant of LBBAP performance: sarcoplasmic reticulum calcium cycling, ion channel expression, connexin-43 gap junction function, and interstitial septal fibrosis. To our knowledge, this is the first review to specifically examine hypothyroidism in the context of LBBAP. The thyroid–LBBAP interaction is biologically plausible and clinically important, but direct clinical validation is absent. Prospective studies are required before formal clinical recommendations can be issued.

If the hypothesis advanced here is confirmed in prospective data, routine thyroid function screening before elective LBBAP — poorly implemented in current practice despite guideline endorsement [10] — could be formalised as a standard pre-procedural step, with structured thyroid optimisation for overt hypothyroid patients. This intersection of internal medicine and cardiac electrophysiology is precisely the type of hypothesis-generating, clinically grounded research that South Asian EP centres are uniquely positioned to investigate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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