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# Cardiac vagal decoupling: a conceptual basis for reflex-independent hemodynamic management under general anesthesia

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Intraoperative hypotension is consistently associated with postoperative organ injury, and recent consensus statements emphasize maintaining mean arterial pressure above pragmatic “harm thresholds” in at-risk patients. Under balanced anesthesia, hypotension often arises in bradycardia-predominant contexts in which reflex pressure–heart rate coupling remains variably expressed. In such settings, reflex sinus slowing can complicate vasoactive titration and contribute to sequence-dependent, non-linear pressure–heart rate trajectories, particularly when vasopressors are followed by antimuscarinics. Here we present cardiac vagal decoupling as a conceptual framework for interpreting—and, when clinically appropriate, discussing—hemodynamic baselines in which subsequent pressor titration is less dominated by reflex sinus slowing, without implying abolition of reflex control or recommending a fixed drug sequence. Using atropine as a reference antimuscarinic, we outline why sinus-rate responses can appear abrupt by considering effector-level threshold-like behavior, sinoatrial node excitability near firing threshold, and non-monotonic muscarinic pharmacodynamics at low dose ranges. We then describe two broad, non-exclusive configurations in which atropine may produce little observable chronotropic change: globally reduced autonomic responsiveness vs. context-limited incremental expression within the muscarinic receptor–effector pathway. Finally, we propose a four-pattern heuristic combining atropine “responsiveness” with bedside evidence of reflex pressure–heart rate coupling to organize interpretation when one signal is missing or weakly expressed, while explicitly recognizing surrogate limitations and motivating empirical evaluation.

## KEYWORDS

atropine, autonomic nervous system, autonomic regulation, baroreflex, bradycardia, intraoperative hypotension, vagus nerve, vasopressors

## 1 Introduction

Stabilizing circulation under general anesthesia remains a central challenge in perioperative hemodynamic management. Even brief episodes of intraoperative hypotension are associated with postoperative organ injury and complications across observational syntheses (1–3), and recent statements emphasize maintaining mean arterial pressure (MAP) above harm thresholds in at-risk patients (4, 5). Interest has

accordingly grown in proactive approaches, including prediction-guided management (6, 7). In this article, we take “harm threshold” in a pragmatic bedside sense—as the point at which clinicians typically initiate corrective action—rather than as a patient-specific ischemic threshold. Because individual vulnerability varies with comorbidity and physiologic reserve, our focus is the interpretability of pressure–heart rate trajectories once an intervention is triggered, not the prescription of universal numeric cutoffs.

Intraoperative hypotension is not a single entity. Blood loss, myocardial dysfunction, anesthetic depth, and vasodilation are common contributors and require conventional assessment and treatment. Inadequate analgesia can also influence pressure through more than one pathway: it may lead clinicians to deepen anesthesia or add drugs that reduce vascular tone and cardiac performance; and some surgical or visceral stimuli can recruit vagally mediated cardioinhibitory reflexes that present as abrupt sinus slowing with a pressure fall. The present argument does not compete with this differential diagnosis. Rather, it focuses on a recurring downstream problem: once vasoactive titration is initiated, reflex control can couple arterial pressure and sinus rate so that responses appear nonlinear, complicating bedside interpretation and dose–response reasoning.

This is the setting in which the concept of cardiac vagal decoupling may be useful as an interpretive framework. If functional vagal braking at the sinus node is reduced upstream, subsequent pressor titration may be less vulnerable to abrupt reflex sinus slowing and may become easier to adjust in smaller steps toward the intended pressure target.

## 2 Conceptual basis: baroreflex modulation by anesthetic and vasoactive drugs

At the system level, general anesthesia renders perioperative hemodynamics non-stationary: anesthetic drug exposure and surgical stimulation can shift autonomic tone and reflex gain over minutes, such that arterial baroreflex expression may intermittently oppose vasoactive titration (8, 9). Pure  $\alpha$ -agonist pressors (e.g., phenylephrine) characteristically increase arterial pressure while recruiting baroreflex-mediated sinus slowing (RR-interval lengthening) and, in some settings, can reduce cardiac output despite increasing mean arterial pressure (MAP) (10, 11). When an antimuscarinic drug is introduced on a pressor-defined, high-afterload (high-vascular tone) background, hypertensive overshoot may be amplified. This has been described, for example, when glycopyrrolate accompanies phenylephrine-based management in obstetric spinal anesthesia (12), and when atropine is co-administered with phenylephrine and is followed by marked increases in heart rate and arterial pressure (13).

At the agent level, changes in anesthetic drug exposure—particularly volatile anesthetic concentration—depress baroreflex function in a concentration-dependent manner, thereby weakening compensatory tachycardia (9). Opioid-predominant anesthesia attenuates baroreflex-mediated tachycardia and can bias control toward vagal dominance (14). As selective adjuncts,  $\alpha_2$ -agonists (e.g., dexmedetomidine) produce bradycardia and

show dose/concentration-dependent, sometimes biphasic effects on arterial pressure and vascular resistance, consistent with transient afterload elevation during concentration transitions (15, 16). Taken together, an exposure pattern characterized by a volatile-sparing, opioid-predominant technique—optionally combined with  $\alpha_2$ -agonist exposure—can yield a bradycardia-predominant state in which vasopressor initiation readily recruits baroreflex-mediated sinus slowing and sequence-dependent, non-linear pressure–heart rate trajectories become more clinically apparent (9, 10, 14).

## 3 The concept of cardiac vagal decoupling: definition and rationale

**Definition.** Cardiac vagal decoupling is used here as a conceptual frame for thinking about and, when clinically appropriate, establishing a hemodynamic baseline in which subsequent pressor titration is less dominated by baroreflex-mediated sinus slowing. The intent is not tachycardia *per se*, but improved interpretability—i.e., a baseline in which attempts to raise arterial pressure are less consistently accompanied by reflex sinus-node braking, and therefore tend to align more closely with clinical intent.

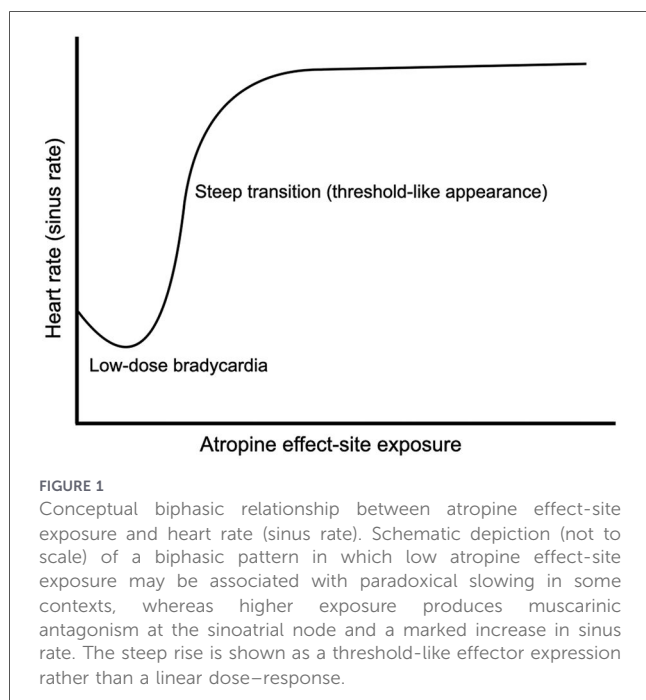
**Rationale—emphasizing the efferent limb.** Under anesthesia, pressor-driven rises in arterial pressure can recruit baroreflex pathways and increase cardiac vagal efferent influence at the sinoatrial node (often alongside sympathoinhibition), thereby coupling pressure increases to sinus slowing and introducing nonlinearity into the observed pressure–HR relationship. Within this frame, “decoupling” refers to attenuating the cardiac vagal efferent contribution to that coupling—by whatever means is clinically appropriate—without implying abolition of reflex control or privileging any specific drug sequence.

## 4 Clinical manifestations of atropine responsiveness and their pharmacophysiological interpretation

In this section, atropine (a muscarinic receptor antagonist) is used as the reference drug to illustrate how reducing functional vagal braking at the sinoatrial node can reshape pressure–heart rate trajectories.

### 4.1 Abrupt heart-rate acceleration after atropine: why responses can look “threshold-like”

Here, “steep transition” is used descriptively to denote an appearance-level phenomenon: a small change in functional muscarinic braking is followed by a disproportionately large change in sinus rate over a short time window (Figure 1). Under anesthesia, vagal input to the sinoatrial node can vary rapidly, and acetylcholine at the effector site is delivered in brief, rapidly cleared pulses. Near the firing threshold of pacemaker activity, these pulse-to-pulse changes in effective muscarinic braking can translate into a non-proportional change



in cycle length, making the pressure–HR trajectory look discontinuous (17–19). Mechanistically, muscarinic (M2) signaling slows pacemaker activity through Gi/o pathways and Gβγ-dependent activation of GIRK channels, providing a substrate in which modest changes in inhibitory current can produce a steep change in net diastolic depolarization rate (20, 21).

At the node level, coupled membrane-voltage and calcium-clock dynamics can further sharpen this effect near threshold, so that releasing inhibition can shift sinus rate abruptly rather than smoothly (22, 23).

Atropine can make this “threshold-crossing” behavior more visible because a bolus can rapidly reduce functional muscarinic braking once sufficient receptor blockade is achieved. Importantly, a large atropine response does not uniquely indicate “low vagal tone”; it may also occur when sympathetic drive or intrinsic chronotropic reserve is high, so the observed step reflects the momentary balance of inputs and effector gain rather than a single latent variable. Finally, atropine itself can show biphasic behavior at low doses and rare paradoxical bradyarrhythmias, which can further complicate bedside interpretation (24–27).

Accordingly, the observed atropine concentration–heart rate relationship at the bedside is not expected to be linear: small additional blockade near a functional threshold can produce a disproportionately large rate change, whereas similar concentration changes away from that threshold may have little visible effect.

## 4.2 “Blunted-response” states: why atropine can appear not to work

Clinically, atropine sometimes produces little or no increase in sinus rate. Importantly, a “blunted response” does not uniquely indicate high vagal tone. Rather, the observed effect is context-dependent and can be shaped by multiple determinants—

including, for example, how much functional muscarinic braking is actually present at the sinoatrial node, the sinus node’s available chronotropic reserve under the prevailing anesthetic state, and the concurrent sympathetic background (drive or sympathoinhibition). With that in mind, several mechanistically distinct configurations can underlie a blunted atropine response; two broad, non-exclusive configurations are outlined below.

- (i) Globally reduced autonomic responsiveness (system-level low gain).

Under some anesthetic states, the overall gain of autonomic cardiovascular regulation is reduced: baroreflex responsiveness, efferent autonomic traffic, and the capacity to change sinus rate are all constrained. In this configuration, both reflex tachycardia and antimuscarinic-evoked increases in heart rate may be small—not because vagal tone is necessarily high, but because the system has limited ability to express a chronotropic change at all. Higher volatile exposure and/or α<sub>2</sub>-agonist exposure are common contributors to this global attenuation (9, 15, 28).

- (ii) Limited incremental sinus-rate change (effector-side limitation).

Even when atropine reaches the effect site, the incremental increase in sinus rate can be modest for at least two non-exclusive reasons. First, there may be little functional muscarinic braking to remove at that moment (i.e., the instantaneous vagal input to the sinoatrial node is already small), so additional muscarinic blockade produces little observable chronotropic change. Second, the translation from receptor blockade to cycle-length shortening can be context-limited at the effector level, such that incremental antagonism produces diminishing changes in net pacemaker behavior. Short-term pharmacodynamic features within the M2–Gi/o–Gβγ–GIRK pathway—including desensitization or effector-pathway saturation—may contribute to this reduced incremental expression (29). In addition, the observable heart-rate change after atropine is shaped by the concurrent sympathetic background and competing inputs to the sinus node; therefore, a small response should not be interpreted as a single-factor readout of “vagal tone” and is more defensibly treated as a context-dependent limitation on how strongly sinus rate can change under the prevailing anesthetic and reflex conditions.

Because these configurations can look similar at the bedside (“atropine didn’t work”), interpretation should avoid a single-factor inference (e.g., “vagal tone must be high/low”). A more conservative reading is that a small observed sinus-rate change reflects limited expressed chronotropic reserve under the current anesthetic and reflex context, further shaped by the sympathetic background.

## 4.3 Conceptual classification of atropine “responsiveness” and bedside evidence of reflex pressure–HR coupling (surrogates)

This scheme is offered as an interpretive heuristic—not a diagnostic taxonomy and not a statement about prevalence. Its

main purpose is to extract interpretive hints when one of the two signals is missing or weakly expressed—i.e., when atropine produces little discernible sinus-rate change and/or when bedside evidence of reflex pressure–HR coupling is not apparent. When both signals are clearly present, the quadrant is included for completeness, but it typically adds less interpretive value because there is no “missing” element to explain.

“Atropine responsiveness” (a discernible rise in sinus rate after dosing) does not uniquely index baseline vagal tone. The observed response reflects the momentary balance between parasympathetic restraint, sympathetic background, and intrinsic sinus-node rate, and it can be shaped by dose/timing and competing reflex inputs (30, 31). Moreover, atropine effects can be non-monotonic across dose ranges in some settings, such that low-dose exposure may increase indices of vagal modulation while higher exposure produces the expected vagolytic chronotropic effect—underscoring that “responsiveness” should be interpreted cautiously and contextually rather than as a single-axis marker of vagal tone (24–26). Likewise, “reflex coupling” here refers only to bedside evidence of pressure–HR coupling (e.g., pressure rises accompanied by sinus slowing) rather than formal physiologic measurement of baroreflex function; the purpose is to organize what a response pattern may suggest about the autonomic context at that moment, while avoiding mechanistic over-interpretation.

#### (A) Minimal responsiveness × minimal coupling

This pattern suggests that heart-rate modulation is not clearly expressed or is difficult to interpret at that moment (e.g., deeper anesthetic state, strong sympatholysis,  $\alpha_2$  exposure, rhythm/measurement limitations, or overlapping interventions). In this setting, the observed chronotropic response after atropine may be small even when muscarinic antagonism is present; interpretation of pressor dose–response should therefore emphasize conventional determinants (preload, afterload, contractility) while explicitly noting major co-interventions and potential confounders.

At first glance, this quadrant might be expected to yield a more “linear-looking” pressor dose–pressure relationship because reflex-linked sinus slowing is not clearly expressed. However, because the defining feature is reduced readability of heart-rate modulation (low autonomic gain and/or substantial confounding), apparent linearity is not a reliable inference, and the pressure response may still be mechanistically ambiguous.

#### (B) Minimal responsiveness × coupling present

When bedside evidence of reflex pressure–HR coupling appears present but the incremental sinus-rate response after atropine is small, the key interpretive difficulty is that “insufficient atropine” and context-dependent limitation of effector expression can look similar at the bedside. One plausible explanation is reduced effector responsiveness within the muscarinic pathway under the current context (e.g., context-dependent pharmacodynamic limitation), although alternative explanations—including dose/timing mismatch, competing reflex inputs, and measurement issues—must also be considered.

Because these possibilities are hard to disentangle without a change in context, repeated short-interval boluses in an otherwise unchanged setting may add limited interpretive value and can make causal attribution more difficult. In this quadrant, it is often more coherent to document the pattern and reassess after salient determinants of coupling and chronotropic expression have changed (e.g., anesthetic depth/exposure, ventilation/ $\text{CO}_2$ , stimulation/analgesia balance, co-vasoactives), rather than treating the observation as evidence of atropine “under-dosing” in isolation.

#### (C) Responsiveness present × coupling present— Reference pattern

Both an atropine-associated rise in sinus rate and bedside evidence of reflex pressure–HR coupling are evident. Because neither signal is missing, this pattern often provides fewer additional interpretive cues than patterns with absent or blunted responsiveness and/or coupling. Importantly, this pattern does not contradict the decoupling concept: cardiac vagal decoupling is not defined as abolishing baroreflex coupling, but as reducing functional vagal braking enough that pressor titration is less dominated by reflex sinus slowing. Thus, detectable coupling may still coexist with a clinically useful degree of decoupling, depending on context.

#### (D) Responsiveness present × minimal coupling

A clear atropine-associated rise in sinus rate suggests that muscarinic restraint at the sinoatrial node was functionally expressed at that moment. If bedside evidence of reflex pressure–HR coupling is nevertheless not apparent, the pattern may appear consistent with disproportionate attenuation of baroreflex afferent signaling and/or central integration while the sinoatrial muscarinic effector remains responsive. However, such a selective configuration is physiologically specialized and should not be inferred casually from routine records. In practice, an “absent coupling” impression can also arise from surrogate limitations and confounding—e.g., pressure perturbations that are too small or poorly timed, or overlapping changes in stimulation, ventilation/ $\text{CO}_2$ , anesthetic depth, and co-administered vasoactives that obscure reflex structure. Accordingly, this quadrant is best treated as an indeterminate pattern unless the pressure stimulus and observation window are sufficiently well defined.

## 5 Discussion

### 5.1 Clinical implications of cardiac vagal decoupling

Cardiac vagal decoupling is best regarded as a way of organizing hemodynamic reasoning rather than a standing order. Under many contemporary anesthetic combinations, reflex-mediated sinus slowing can become a practical obstacle when hypotension arises in a bradycardia-predominant state on a relatively vasoconstricted background. In that context, treating functional vagal influence at the sinoatrial node as a modifiable determinant helps explain why common reactive sequences

(pressor escalation followed by later antimuscarinics) may yield modest, variable, or internally inconsistent pressure–HR trajectories.

Within this framework, a decoupling-oriented baseline can be considered before substantial pressor escalation in a subset of cases—particularly when (i) hypotension coexists with bradycardia or a low sinus rate that plausibly limits flow, and (ii) bedside observations remain consistent with reflex pressure–HR coupling (e.g., pressure rises accompanied by sinus slowing), under an anesthetic background in which volatile agents and opioids, with or without adjunctive  $\alpha_2$ -agonists, plausibly shape autonomic gain. The aim is not to enforce tachycardia, but to establish a baseline in which subsequent adjustments of preload, vascular tone, and contractility are less likely to be repeatedly opposed by reflex sinus slowing, and in which antimuscarinics introduced after pressor initiation are less likely to coincide with abrupt trajectory discontinuities.

The four logical patterns combining atropine “responsiveness” and bedside evidence of reflex coupling (Table 1) are positioned as interpretive aids once atropine has been used during

hemodynamic management: they summarize what an observed response (or non-response) may suggest about the autonomic context at that moment, without prescribing a specific drug sequence.

This framework remains subordinate to generic hemodynamic priorities. It is less informative or less attractive when it predictably magnifies arterial pressure or does not address the limiting factor—for example, during  $\alpha_2$ -agonist concentration transitions with high vascular tone (risk of excessive hypertension), in advanced intrinsic atrioventricular block without pacing access (rate limited by conduction), in fixed-output lesions (rate changes do not improve forward flow), in profound hypovolemia (volume deficit predominates), or under intense  $\beta$ -blockade (limited sympathetic reserve).

Predicting an individual patient’s response to hypotension or vasopressor challenge is inherently limited by state dependence: the same patient can show different pressure–HR coupling as anesthetic depth, ventilation/ $\text{CO}_2$ , surgical stimulation, temperature, and adjunct drug exposure change. Nevertheless,

TABLE 1 Logical patterns combining atropine “responsiveness” and bedside evidence of reflex pressure–HR coupling under anesthesia.

| Pattern  | Atropine “responsiveness” <sup>a</sup> | Bedside evidence of reflex pressure–HR coupling <sup>b</sup> | Interpretation (conservative)   |
|--|--|--|---|
| (A) Minimal responsiveness $\times$ minimal coupling                   | Absent or minimal HR rise              | No clear coupling pattern/<br>markedly blunted               | HR modulation and reflex structure are weakly expressed or difficult to interpret in the current context (e.g., reduced autonomic gain, measurement/rhythm limitations, or substantial confounding co-interventions). Apparent “linearity” of pressor dose–pressure should not be assumed from the absence of visible coupling.   |
| (B) Minimal responsiveness $\times$ coupling present                   | Absent or minimal HR rise              | Coupling pattern remains visible                             | Reflex coupling appears present, but incremental sinus-rate change after atropine is small. “Insufficient atropine” and context-dependent limitation of effector expression can look similar; alternative explanations include dose/timing mismatch, competing reflex inputs, and measurement limitations.  |
| (C) Responsiveness present $\times$ coupling present—Reference pattern | Clear HR rise                          | Coupling pattern visible                                     | Both signals are expressed. Included for completeness; often provides fewer additional interpretive hints because neither signal is missing. Compatible with the decoupling concept: detectable coupling may still coexist with a clinically useful reduction in reflex-dominant sinus slowing, depending on context.   |
| (D) Responsiveness present $\times$ minimal coupling                   | Clear HR rise                          | No obvious coupling pattern                                  | Pattern may appear consistent with attenuated baroreflex afferent/central expression with preserved sinoatrial muscarinic effector responsiveness, but such selectivity is physiologically specialized and should not be inferred casually from routine records. “Absent coupling” impressions are also vulnerable to surrogate limitations and confounding (e.g., small/poorly timed pressure perturbations, overlapping changes in stimulation, ventilation/ $\text{CO}_2$ , anesthetic depth, and co-vasoactives). Treat as indeterminate unless the perturbation and observation window are well defined. |

<sup>a</sup>Atropine “responsiveness” refers to an observed rise in sinus rate after dosing; it does not uniquely index baseline vagal tone and may also reflect high sympathetic drive with residual vagal restraint, timing/dose effects, or competing reflex inputs.

<sup>b</sup>“Reflex coupling” is inferred from bedside surrogates and does not imply formal baroreflex testing; absence of a surrogate pattern does not prove reflex absence, and decoupling does not require abolition of reflex coupling.

preoperative information can provide useful context once hypotension management is initiated. Baseline heart rate/rhythm and conduction status, chronic autonomically active medications (e.g.,  $\beta$ -blockers), features suggestive of limited chronotropic reserve or autonomic dysfunction, and the planned anesthetic exposure pattern (e.g., volatile-sparing opioid-predominant techniques with or without  $\alpha_2$ -agonists) may influence how readily reflex sinus slowing is expressed during pressor steps or how abruptly sinus rate changes after antimuscarinic dosing. In this framework, such information supports interpretation rather than a fixed intraoperative sequence; the evolving intraoperative pressure–HR trajectory remains the main basis for reassessing autonomic context as conditions change.

## 5.2 Future directions

This framework is empirically testable and motivates two working hypotheses.

First, if reflex constraints meaningfully contribute to nonlinear pressure–heart rate trajectories under general anesthesia, then establishing a hemodynamic baseline with reduced functional vagal braking before substantial vasoactive escalation may be associated with weaker pressor-linked sinus slowing and a more proportional vasoactive dose–response. This could be examined by relating standardized pressor steps to paired changes in sinus rate and arterial pressure using prespecified pre/post windows.

Second, if hypertensive surges after late antimuscarinic dosing reflect abrupt removal of sinus-node vagal restraint on a high-vascular tone background, then earlier reduction of functional vagal braking may be associated with fewer or smaller post-antimuscarinic hypertensive overshoots compared with reactive sequencing (pressor first, antimuscarinic later). This could be quantified using peak MAP relative to a predefined clinical target range and/or time above that range within a prespecified post-dose interval.

These hypotheses are approachable using observational datasets and pragmatic trials based on routinely recorded hemodynamic variables and clinically relevant endpoints (e.g., vasoactive exposure, time to hemodynamic stability, and adverse events). Until such evidence is available, cardiac vagal decoupling is best presented as a physiologically grounded interpretive lens rather than as a prescriptive algorithm.

## 5.3 Conclusion

Arterial baroreflexes are indispensable in the awake state, yet under contemporary general anesthesia their heart-rate component can sometimes counteract intended hemodynamic management—particularly in bradycardia-predominant contexts where pressor-associated rises in arterial pressure are accompanied by sinus slowing and subsequent antimuscarinic dosing can produce abrupt changes in the paired pressure–heart rate response. In this article, we present cardiac vagal decoupling as a conceptual framework that treats functional vagal braking at the sinoatrial node as a clinically relevant

constraint to consider explicitly when interpreting pressure–heart rate responses. The aim is not to promote tachycardia or to recommend a fixed drug sequence, but to improve the interpretability of vasoactive titration by reducing the likelihood that reflex-mediated sinus slowing dominates the observed response once intervention is underway. Whether this framework improves hemodynamic management beyond current reactive practice is an empirical question that will require prospective evaluation. Until such evidence is available, cardiac vagal decoupling is best presented as a physiologically grounded way to organize hemodynamic reasoning under anesthesia rather than as a prescriptive protocol.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## Author contributions

SN: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. The author used a generative AI tool (OpenAI; ChatGPT GPT-5.1 Thinking) to assist in refining English phrasing, checking logical consistency, and supporting literature exploration. All cited sources were verified against the

original publications, and all scientific content, interpretations, and conclusions were conceived and confirmed by the author, who takes full responsibility for the work.

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