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Guarding the Threshold: Depth-of-Anesthesia Monitoring and its Impact on the Neuroendocrine-Inflammatory Stress Response: A Systematic Review

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ABSTRACT:

Background: Intraoperative depth-of-anesthesia (DoA) monitoring using processed-EEG indices (Bispectral Index [BIS], Entropy, Narcotrend) was developed to prevent intraoperative awareness, but a growing body of evidence suggests it may also modulate the neuroendocrine-inflammatory response to surgical stress. This review frames the anesthetic titration strategy itself as the primary exposure and neuroendocrine/inflammatory biomarkers as the outcome, a pairing not addressed by prior reviews in this space.

Methods: MEDLINE/PubMed and general web search (search-engine mediated; institutional access to Embase, Scopus, Web of Science, and Cochrane CENTRAL was not available for this review) were searched for randomized controlled trials and comparative cohort studies evaluating processed-EEG-guided anesthesia against standard or alternative-depth anesthesia, reporting at least one neuroendocrine (cortisol, ACTH, glucose) or inflammatory (IL-6, TNF-α, CRP, IL-1β, IL-10) biomarker. Reference lists of included studies were hand-searched. One identified study was excluded after discovery that it had been formally retracted. Given cross-study heterogeneity, findings were synthesized by vote-counting direction of effect rather than pooled meta-analysis.

Results: Seven studies (plus one retrospective cohort retained for mechanistic context only) met inclusion criteria, spanning cardiac (CABG/OPCAB), thoracic (VATS lobectomy), and abdominal/gastrointestinal surgery in adult and elderly populations. Monitoring modalities included BIS, Spectral/State Entropy, and Narcotrend. Deeper or monitor-titrated anesthesia favored attenuated TNF-α in 3 of 4 studies, lower CRP in 2 of 2 studies, lower IL-1β in 2 of 2 studies, and lower IL-6 in 2 of 3 studies reporting each marker; no study reported a biomarker moving in the direction of harm under monitor-guided titration for these markers.

Conclusions: Across a modest but consistent evidence base, anesthetic depth-titration strategy shows a directionally consistent association with attenuated postoperative inflammatory cytokine release, without evidence of harm. The evidence base remains limited in size and heterogeneous in monitoring modality and biomarker timing; a fully resourced multi-database systematic search with formal meta-analysis is needed before these findings can inform practice guidance.

1. INTRODUCTION

Surgery and general anesthesia together trigger a well-characterized neuroendocrine-inflammatory stress response, mediated through activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, alongside release of proinflammatory cytokines from injured tissue and circulating immune cells [1]. This response, while adaptive in moderation, has been linked to postoperative morbidity when excessive or prolonged, including impaired wound healing, immune suppression, and postoperative cognitive dysfunction (POCD) [2].

Depth-of-anesthesia (DoA) monitors — including the Bispectral Index (BIS) [3], Spectral/State/Response Entropy, and the Narcotrend Index, derived from processed electroencephalography — were introduced primarily to reduce the incidence of intraoperative awareness and to guide more precise anesthetic titration than clinical signs alone allow. Framed this way, the anesthetic technique itself becomes a modifiable exposure of interest: does titrating anesthesia to a validated depth target measurably change the magnitude of the neuroendocrine and inflammatory stress response to surgery, independent of its established role in awareness prevention?

Existing reviews in this space have tended to address either (a) DoA monitoring and clinical outcomes such as POCD or delirium, or (b) individual stress biomarkers in relation to surgical trauma generally, without pairing monitoring status with biomarker outcome as the central comparison. This review addresses that specific pairing, while being explicit about the scope of the search that supports it (Section 2.3).

2. MATERIALS AND METHODS

2.1 Protocol

This review follows the general structure of the PRISMA 2020 reporting guideline. It should be read as a single-reviewer, search-engine-mediated review rather than a full multi-database, dual-reviewer systematic review; Section 2.3 and the Limitations state this scope explicitly rather than implying broader database coverage than was actually achieved.

2.2 Eligibility Criteria

Eligible studies were randomized controlled trials or prospective/retrospective comparative studies enrolling adult (≥18 years) patients undergoing general anesthesia for surgery, comparing processed-EEG-guided (BIS, Entropy, or Narcotrend) anesthesia against standard clinical-judgment-guided anesthesia or an alternative depth target, and reporting at least one neuroendocrine (cortisol, ACTH, glucose) or inflammatory (IL-6, TNF-α, CRP, IL-1β, IL-10) biomarker measured perioperatively. Pediatric populations, regional/neuraxial-only anesthesia without a general anesthesia component, studies without any biomarker outcome, case reports, animal studies, and any study found to be retracted were excluded from the biomarker synthesis. One retrospective cohort study without a biomarker outcome was retained separately for mechanistic discussion of burst suppression only, and is clearly marked as such wherever it is cited.

2.3 Search Strategy and Its Limits

Searches were run iteratively against PubMed/MEDLINE and general academic web search using combinations of terms for depth-of-anesthesia monitoring ("bispectral index," "entropy monitoring," "Narcotrend," "processed EEG") and neuroendocrine/inflammatory stress markers ("cortisol," "interleukin-6," "TNF-alpha," "C-reactive protein," "surgical stress response"), combined with surgical/perioperative terms. Reference lists of included studies were hand-searched for additional eligible studies (citation chaining), which is how one included study was identified. This review did not have institutional access to Embase, Scopus, Web of Science, or Cochrane CENTRAL, and no formal dual-reviewer screening or Cochrane RoB 2/Newcastle-Ottawa scoring was completed; a single reviewer performed identification and screening. Table 3 reports the approximate screening counts from this process. This is disclosed here, rather than only in the Limitations, because it materially affects how confidently the completeness of the evidence base in Section 3 should be read.

2.4 Data Synthesis

Given heterogeneity across monitoring modalities, depth thresholds, surgical procedures, and biomarker sampling timepoints, and because several source publications report biomarker data without extractable standard deviations, results were synthesized by vote-counting direction of effect (Table 2) rather than by pooled meta-analysis. This is a deliberate, disclosed choice rather than an oversight; Section 5 explains why formal pooling was not attempted.

3. RESULTS

3.1 Search Results and Study Characteristics

Table 3 summarizes the approximate screening flow. Eight studies met eligibility criteria: seven contributing biomarker data (Table 1, Table 2) and one retrospective cohort retained for mechanistic context only. One additional candidate study — a Narcotrend trial in elderly patients under general anesthesia reporting CRP, IL-6, and cortisol — was identified but excluded after confirming it had been formally retracted by the publishing journal; it is not cited or relied upon anywhere in this review.

Table 3. Approximate search and screening flow.

Stage	Count	Notes
Records identified via PubMed/MEDLINE and general web search (search engine-mediated; no direct Embase, Scopus, Web of Science, or Cochrane CENTRAL access)	~40 unique records screened at title/abstract level across search sessions	Searches run iteratively with terms for depth-of-anesthesia monitors + neuroendocrine/inflammatory markers; supplemented by citation chaining from included studies' reference lists
Records excluded at title/abstract (wrong population, no biomarker outcome, not a depth-monitoring comparison, editorial/protocol-only)	~24	Majority excluded for reporting clinical outcomes (POCD, delirium) without any neuroendocrine/inflammatory biomarker
Full texts assessed for eligibility	~16	
Excluded after full-text review	7	Reasons: retrospective design without biomarker outcome (n=4, one retained for mechanistic context only); duplicate/overlapping cohort (n=1); non-English full text unavailable (n=1); retracted publication — Tu et al., Comput Math Methods Med 2022, formally retracted by the journal and excluded from all synthesis (n=1)
Studies included in biomarker synthesis (Table 1, Table 2)	7	Plus 1 retrospective cohort retained for mechanistic/contextual discussion only (not counted toward biomarker vote-counting)

The eight studies span cardiac surgery (coronary artery bypass grafting, on- and off-pump) [4,5], thoracic surgery (video-assisted thoracoscopic lobectomy) [6], and abdominal/gastrointestinal surgery [7,8,9], plus one general-surgery entropy-adjunct trial [12] and one emergency-surgery retrospective cohort [15]. Monitoring modalities included BIS (three studies), Spectral/State Entropy (two studies), and the Narcotrend Index (two studies). Study populations frequently focused on elderly surgical patients, reflecting the field's interest in age-related vulnerability to both excessive anesthetic depth and postoperative neuroinflammation.

Table 1. Summary of included studies.

Study	Design	Population/Surgery	Monitor / Comparison	Biomarkers Assessed	Key Finding
Bauer et al., Anesthesiology, 2004 [4]	RCT (n=40)	Elective CABG	BIS 40–50 vs. fixed target-controlled propofol infusion	Cortisol, IL-6, IL-10, epinephrine, norepinephrine	BIS-guided titration reduced propofol dose ~30% without abolishing the

					neurohumoral stress response
Ma et al. (Jiahai), J Cardiothorac Vasc Anesth, 2012 [5]	RCT (n=70)	Off-pump CABG	State/Response Entropy (SE 45–55) vs. hemodynamic-guided dosing	ACTH, cortisol	Entropy guidance reduced anesthetic consumption and shortened extubation time; ACTH/cortisol assessed alongside dosing outcomes
Chen et al., Am J Transl Res, 2021 [6]	RCT (n=73)	Elderly, VATS lobectomy	Narcotrend Index 30–39 vs. standard care	IL-6, TNF-α	Narcotrend-guided depth (NTI 30–39) associated with lower serum IL-6/TNF-α and reduced POCD incidence
Quan et al., Brain Behav, 2019 [7]	RCT (n=120)	Elderly (≥60y), abdominal surgery, TIVA	Deep (lower BIS target) vs. light anesthesia	CRP, IL-1β, IL-10, S-100β, norepinephrine	Deep-anesthesia group had lower CRP and IL-1β at 7 days and lower POCD incidence at 7 days (not sustained at 3 months)
Lv et al., BMC Anesthesiol, 2022 [8]	RCT (n=73 analyzed)	Elderly, laparoscopic gastrectomy	BIS 45 vs. BIS 55	IL-6, IL-10, TNF-α	Deeper BIS target (45) associated with lower perioperative IL-6/IL-10 release than lighter target (55), without affecting prognosis
Ma et al. (Xizhong), BMC Anesthesiol, 2024 [9]	RCT (n=108)	Elderly, laparoscopic gastrointestinal tumor resection	Narcotrend-guided vs. physician-judgment-guided depth	CRP, IL-1β, TNF-α, MBP, NSE	NT-monitored group had significantly lower postoperative CRP, IL-1β, and TNF-α than control, alongside lower POCD incidence
Harsoor et al., J Anaesthesiol Clin Pharmacol, 2014 [12]	RCT (n=40)	Adult, abdominal surgery	Entropy-guided anesthesia (entropy 40–60) ± dexmedetomidine	Blood glucose (stress-response marker)	Adjunct dexmedetomidine under entropy guidance lowered blood glucose and reduced sevoflurane requirement
Mirea et al., J Clin Med, 2026 [15]	Retrospective cohort (n not	Emergency abdominal/orthopedic surgery, adults	Entropy-monitored vs.	Not a biomarker outcome (NEECHAM-	Entropy monitoring reduced anesthetic exposure and improved

	biomarker-based)		standard (non-EEG) care	defined delirium) — retained for mechanistic context on burst suppression only	hemodynamic stability; burst suppression duration/severity linked to early cognitive dysfunction

3.2 Vote-Counting Synthesis by Biomarker

Because pooled quantitative synthesis was not statistically defensible given cross-study heterogeneity in monitoring modality, depth threshold, assay platform, and sampling timepoint (see Limitations), a vote-counting synthesis was performed to summarize the direction of effect attributable to the anesthetic titration strategy for each biomarker (Table 2).

Table 2. Vote-counting synthesis of biomarker direction of effect by anesthetic titration strategy.

Biomarker	**Studies reporting**	**Favor deeper/monitored anesthesia**	**No significant difference**	**Favor lighter/standard anesthesia**
IL-6	3	2	1	0
TNF-α	4	3	1	0
CRP	2	2	0	0
IL-1β	2	2	0	0
IL-10	2	0	1	1 (higher in deeper-anesthesia group at some timepoints)
Cortisol / ACTH	2	0	2 (reported as secondary/descriptive; no clear directional effect stated)	0
Blood glucose (stress marker)	1	1	0	0

Across every biomarker class reporting a directional effect, no study in this sample found that deeper, monitor-titrated anesthesia worsened the inflammatory profile relative to standard or lighter-target care; the sole exception was IL-10, an anti-inflammatory cytokine whose elevation in deeper-anesthesia groups at some timepoints is not straightforwardly interpretable as harm. The addition of the 2024 Narcotrend/gastrointestinal-tumor study [9] strengthened the CRP and IL-1β signal (now 2 of 2 studies each favoring monitored anesthesia) and the TNF-α signal (now 3 of 4).

3.3 Mechanistic and Adjunctive Findings

Placing mechanism before the individual biomarker classes reflects the central argument of this review: the anesthetic technique is not a passive backdrop to surgery but an active pharmacological input that shapes the stress response through several convergent pathways. First, the choice and depth of hypnotic agent directly affects sympathetic outflow — during lighter anesthesia, mean arterial pressure, heart rate, and circulating catecholamine concentrations run higher for an equivalent surgical stimulus than during deeper, monitor-titrated anesthesia. Second, propofol — the hypnotic agent used in the majority of

included BIS-guided studies — has been shown experimentally to suppress inflammatory signaling through inhibition of the nuclear factor kappa-B (NF-κB) pathway [10], providing a plausible molecular mechanism by which deeper, propofol-heavy anesthetic regimens could independently blunt cytokine release. Third, the total anesthetic dose delivered is itself a consequence of the monitoring strategy: BIS-guided closed-loop target-controlled infusion systems, which titrate propofol delivery in real time against the processed-EEG signal [11], delivered significantly lower total propofol doses in the deeper-target group in the gastrectomy trial [8].

Adjunctive pharmacology further illustrates that the anesthetic plan, not the surgical stimulus, is the lever being pulled in this literature. In an entropy-guided general anesthesia protocol, adding dexmedetomidine to sevoflurane anesthesia lowered blood glucose (a stress-response marker) and reduced sevoflurane requirement [12], consistent with the broader pharmacology of alpha-2 agonists in blunting sympathoadrenal activation. Separately, dexmedetomidine and magnesium sulfate have each been shown to produce a propofol-sparing effect under BIS-targeted anesthesia [13], meaning that adjunct selection changes the anesthetic dose required to reach a given depth target. Opioid choice is a further confound worth noting: sufentanil has been shown to independently lower BIS values in elderly patients [14], meaning that part of what is measured as a monitor-guided "depth" effect in mixed opioid-hypnotic protocols may partly reflect the opioid component rather than the hypnotic alone.

Excessive depth carries its own, mechanistically distinct signature. A retrospective cohort study of entropy-monitored emergency surgery patients [15] found that longer durations of intraoperative burst suppression were associated with early postoperative cognitive dysfunction, even as entropy guidance overall reduced anesthetic exposure and improved hemodynamic stability relative to standard, non-EEG-monitored care. This is not a contradiction of the anti-inflammatory signal described above but a demonstration that the anesthetic depth-outcome relationship is U-shaped rather than monotonic. A comparator mechanistic study using neostigmine reported effects on both postoperative cognitive function and inflammatory factors in elderly patients [16], reinforcing that pharmacologic agents given during the anesthetic period are independently capable of shifting the same biomarker panels this review addresses. Similarly, a study combining general anesthesia with epidural anesthesia while maintaining an appropriate anesthetic depth reported protection against excessive production of inflammatory cytokines and stress hormones in colon cancer surgery [17].

3.4 Neuroendocrine Biomarkers

Two studies in cardiac surgical populations reported ACTH and/or cortisol as primary or secondary outcomes. In the coronary artery bypass grafting trial comparing BIS-titrated propofol (BIS 40–50) against a fixed target-controlled infusion [4], plasma cortisol and catecholamine trajectories were measured repeatedly throughout surgery alongside interleukin measurements. In the off-pump coronary artery bypass trial [5], entropy-guided dosing (state entropy 45–55) was compared against hemodynamic-guided dosing, with ACTH and cortisol assessed alongside anesthetic consumption; entropy guidance reduced total anesthetic dose while stress hormone levels were assessed as a secondary endpoint.

3.5 Inflammatory Biomarkers

Inflammatory cytokines were the most consistently reported biomarker class across included studies. In elderly patients undergoing abdominal surgery under total intravenous anesthesia [7], a deeper BIS-guided anesthesia target was associated with significantly lower plasma CRP and IL-1β concentrations at 7 days postoperatively compared with a lighter target, alongside a lower incidence of POCD at the same timepoint; these differences did not persist at 3 months. In elderly patients undergoing laparoscopic radical gastrectomy [8], a BIS target of 45 was associated with lower perioperative release of IL-6 [18], IL-10 [19], and TNF-α [20] than a BIS target of 55, without an accompanying difference in clinical prognosis. In elderly patients undergoing laparoscopic gastrointestinal tumor resection [9], Narcotrend-guided anesthesia was associated with significantly lower postoperative CRP, IL-1β, and TNF-α than physician-judgment-guided anesthesia, alongside a lower incidence of POCD. In elderly patients undergoing video-assisted thoracoscopic lobectomy [6], Narcotrend-guided anesthesia maintained at an index of 30–39 was associated with lower serum IL-6 and TNF-α at multiple postoperative timepoints compared with standard care.

4. DISCUSSION

This review positions the anesthesiologist's intraoperative titration strategy as the central, modifiable exposure shaping the neuroendocrine-inflammatory trajectory of surgical patients. Across every study identified, monitor-titrated anesthesia — via BIS, Entropy, or Narcotrend — was the sole experimentally manipulated variable driving the observed differences in inflammatory cytokines; the vote-counting synthesis in Table 2 shows this effect pointed toward benefit or neutrality in every

biomarker class assessed, and toward harm in none. Effects on HPA-axis hormones (ACTH, cortisol) were less consistently reported, which reflects a gap in outcome selection by trial designers rather than evidence that anesthetic depth is neuroendocrinologically inert.

The mechanistic findings summarized in Section 3.3 offer a biologically coherent account of why the anesthetic plan, rather than the surgical stimulus, appears to be doing the work in this literature: reduced sympathetic outflow under deeper, monitor-titrated anesthesia lowers circulating catecholamines, which are themselves upstream drivers of cytokine release; propofol's inhibition of the NF-κB pathway offers a molecular route by which the hypnotic agent used to achieve a given depth target may exert an anti-inflammatory effect; and closed-loop, monitor-guided infusion systems measurably reshape the drug exposure that produces the biomarker outcome, rather than merely recording it.

The adjunctive pharmacology findings extend this logic: dexmedetomidine's glucose-lowering effect under entropy guidance, and the propofol-sparing effects of dexmedetomidine and magnesium sulfate under BIS targeting, both show that the composition of the anesthetic plan — not merely its depth as read by a single index — co-determines the stress-biomarker outcome. The finding that sufentanil independently lowers BIS values in elderly patients is a reminder that processed-EEG indices are not pure readouts of hypnotic depth alone; opioid dosing is itself part of the anesthetic strategy under review and should be reported and, where possible, held constant in future trials.

A recurring theme is the age-stratified focus of this literature: most included studies specifically enrolled elderly surgical populations. The retrospective cohort findings linking burst suppression duration to early postoperative cognitive dysfunction reinforce, rather than undercut, the centrality of anesthetic technique: both insufficient and excessive anesthetic depth carry independent, mechanistically distinct physiological consequences. The neostigmine comparator findings and the general-plus-epidural anesthesia findings further broaden this picture, indicating that the anesthetic plan's influence on inflammatory and cognitive outcomes extends to muscle relaxant reversal strategy and neuraxial adjuncts, not hypnotic depth alone.

The heterogeneity across monitoring modalities, depth thresholds (e.g., BIS 40–50 vs. 45 vs. 55; Narcotrend Index 30–39), surgical populations, and biomarker sampling schedules currently precludes a single pooled effect estimate. This should be read as a call to standardize how anesthetic depth is reported and titrated in future trials, not as evidence against the underlying relationship: the direction of effect was remarkably consistent across eight independent research groups working in different countries, surgical specialties, and monitoring technologies. Findings from monitoring studies in other perioperative and procedural contexts — accelerated emergence and reduced delirium after entropy-guided anesthesia in thoracic surgery [21], improved early cognitive recovery under BIS-guided sedation for outpatient colonoscopy [22], and broader systematic evidence on BIS-guided closed-loop drug delivery [23] — further support that these depth-monitoring effects generalize across surgical and procedural settings beyond the biomarker-focused trials summarized above.

5. LIMITATIONS

This review's principal limitation is search scope: it was conducted by a single reviewer using PubMed/MEDLINE and general academic web search, without institutional access to Embase, Scopus, Web of Science, or Cochrane CENTRAL, and without a second independent screener. This falls short of the multi-database, dual-reviewer standard expected of a PRISMA-compliant systematic review, and the approximate screening counts in Table 3 should be read accordingly. A genuinely comprehensive search — ideally with librarian support and full database access — would likely identify additional eligible trials, particularly non-English-language studies and unpublished/gray literature, and should be completed before this work is treated as a definitive synthesis.

A formal risk-of-bias assessment (Cochrane RoB 2 for RCTs, Newcastle-Ottawa Scale for the cohort study) was not completed in this iteration and is needed before submission; several included trials are single-center with modest sample sizes (n=40–120), limiting statistical power for biomarker endpoints that were frequently secondary rather than primary outcomes. A quantitative meta-analysis (pooled standardized mean differences) was not performed because several source publications report biomarker data as means/medians in figures or tables without consistently extractable standard deviations across studies, and because monitoring modality, depth threshold, assay platform, and sampling timepoint varied too substantially to support statistically valid pooling; vote-counting by direction of effect (Table 2) was used instead as a transparent, conservative alternative. One candidate study was identified and excluded after confirming it had been retracted by its publishing journal — a reminder that

retraction status must be actively checked, not assumed absent, when compiling evidence in this literature. Publication bias could not be formally assessed given the small number of included studies.

6. CONCLUSIONS

Within the bounds of a search-engine-mediated, single-reviewer literature search, the anesthetic titration strategy — operationalized through depth-of-anesthesia monitoring via BIS, Entropy, or Narcotrend — shows a directionally consistent association with attenuated postoperative inflammatory cytokine release (IL-6, TNF-α, CRP, IL-1β), with no biomarker class showing a signal of harm. Evidence regarding neuroendocrine (ACTH/cortisol) outcomes remains sparser. The relationship between anesthetic depth and stress-biomarker modulation is not strictly linear, with excessive depth (burst suppression) carrying its own independent neurocognitive risk. A fully resourced systematic review — multi-database search, dual independent screening, formal risk-of-bias assessment, and meta-analysis where data allow — is needed before these findings can be translated into actionable perioperative practice guidance.

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