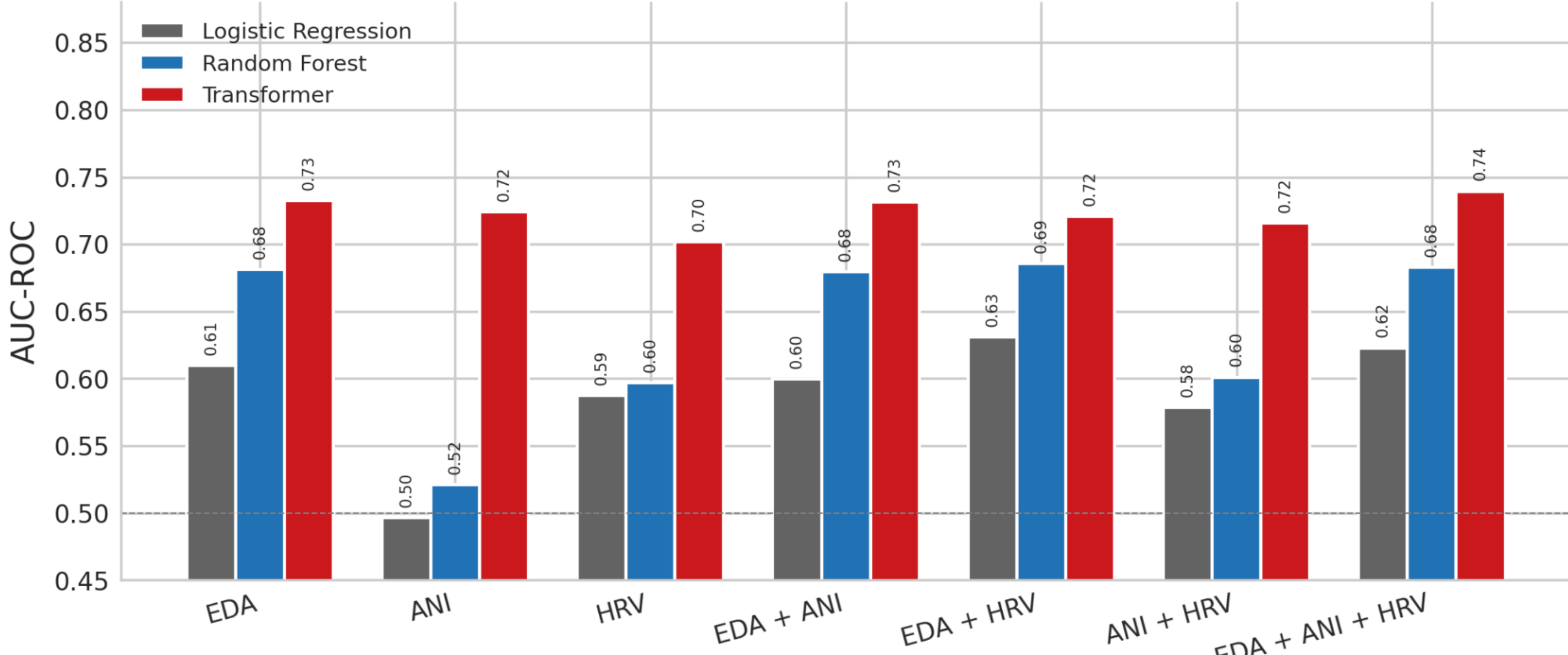
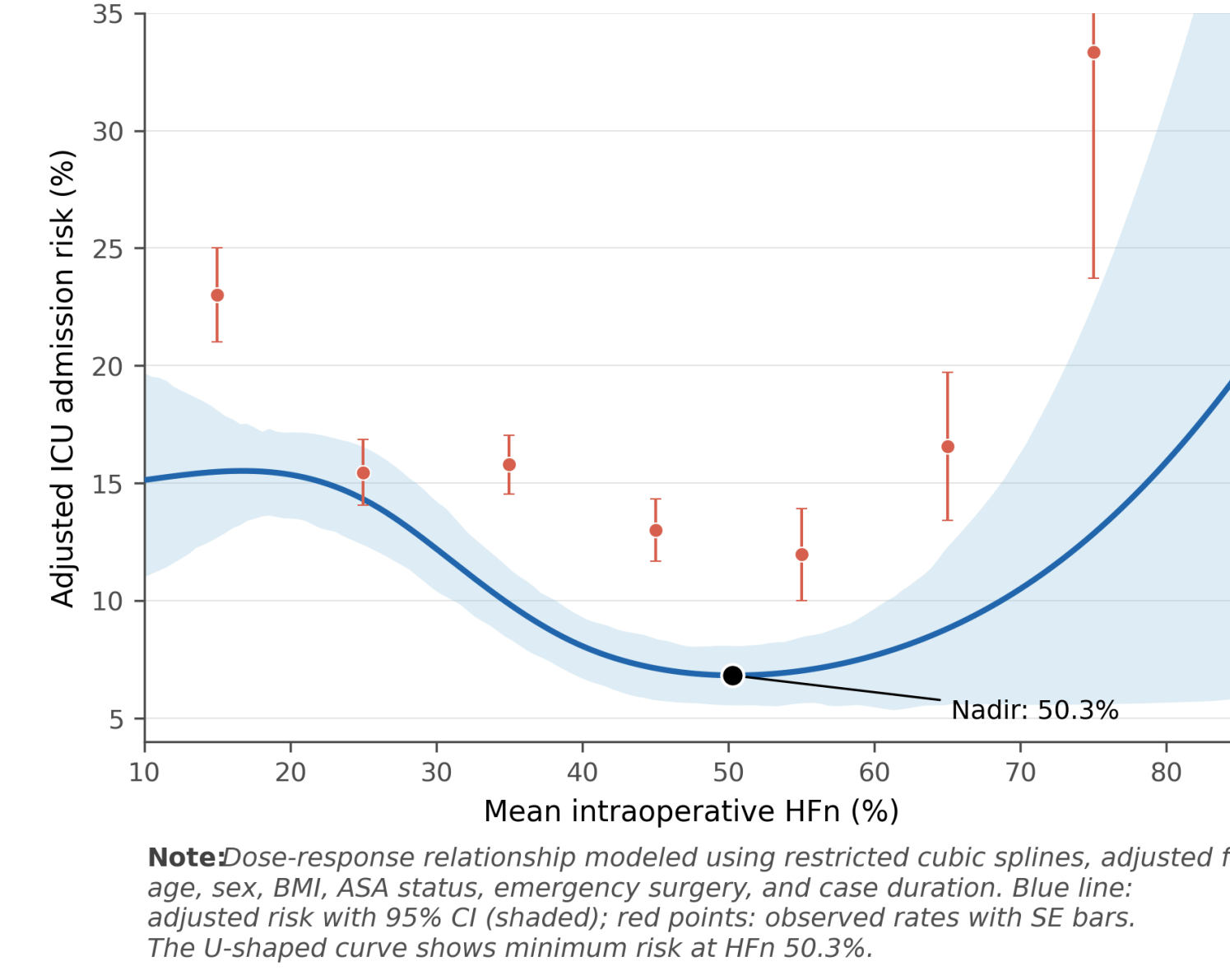
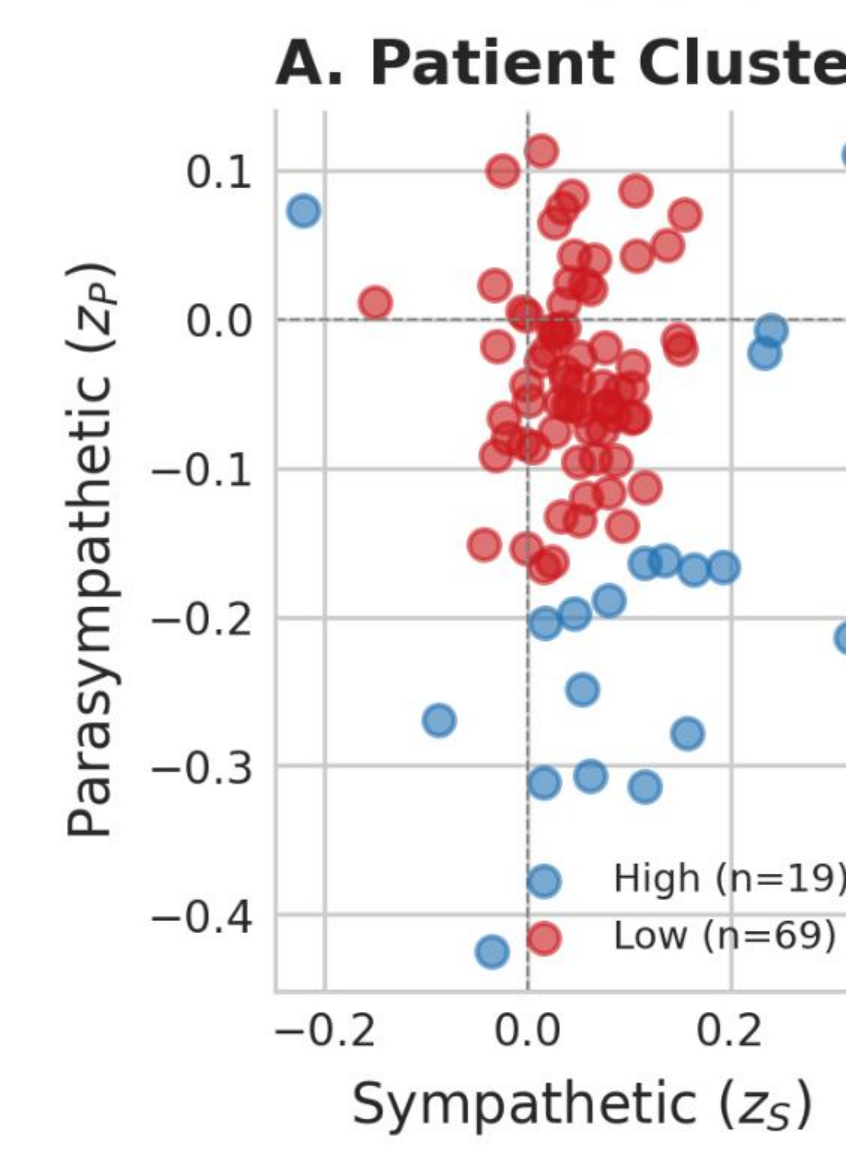
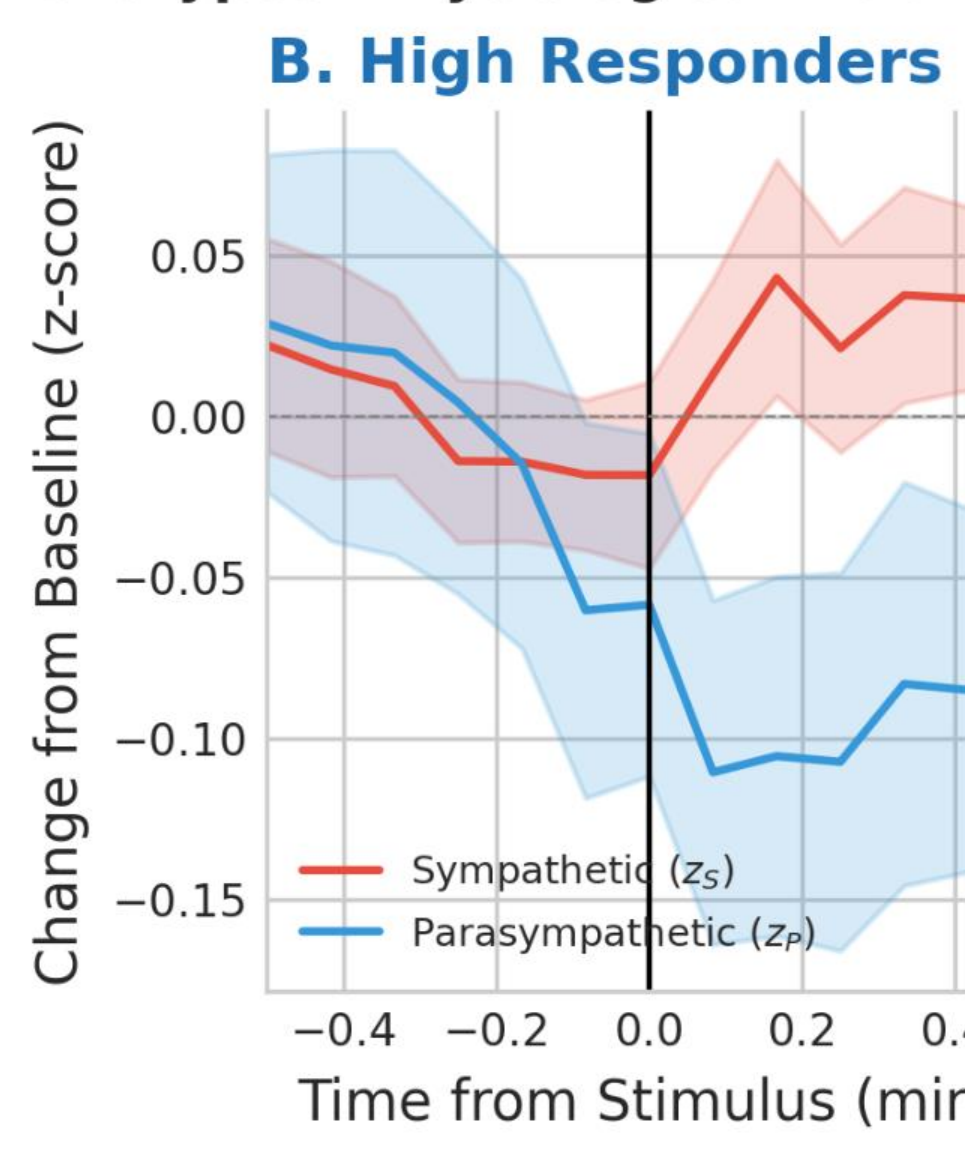
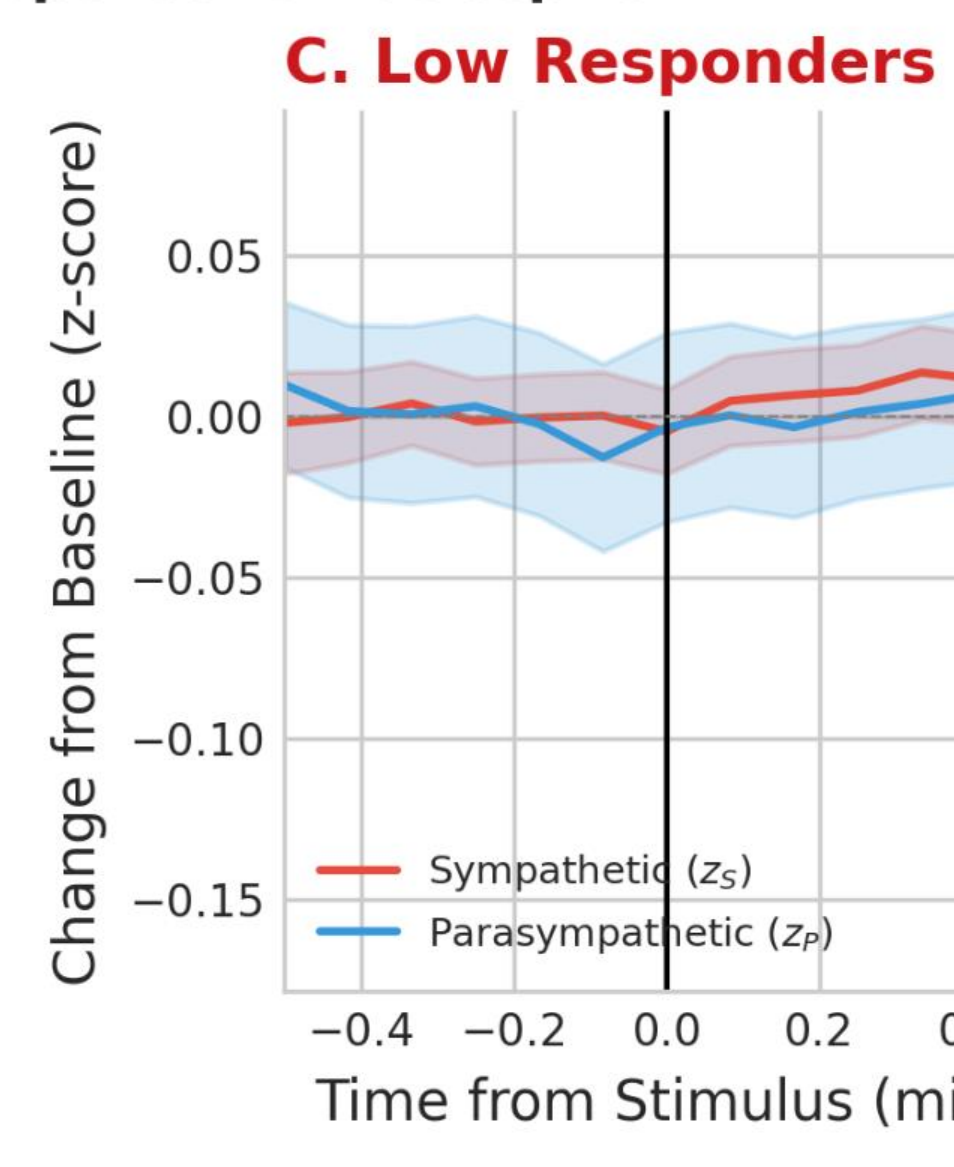


INTRODUCTION	METHODS	HRV & Features	Predicting EDA from HRV and Drug Effects Explored	Results
Adequate analgesia during surgery is critical for patient outcomes, yet reliable intraoperative nociception monitoring remains challenging. The Analgesia Nociception Index (ANI), derived from heart rate variability (HRV) analysis of parasympathetic tone, has become a widely adopted tool for guiding analgesic administration. However, ANI reflects only one component of the autonomic nervous system and may miss sympathetically mediated nociceptive responses. We build on the work of Subramanian et al. (2024) to evaluate the relationship between ANI and EDA and to identify distinct autonomic response phenotypes among surgical patients. Electrodermal activity (EDA), which measures skin conductance changes driven by sympathetic innervation of sweat glands, offers a possible complementary view into autonomic function. While EDA has been studied in pain research, its utility relative to ANI for intraoperative nociception detection remains unclear. Furthermore, whether HRV-derived features could serve as a proxy for EDA—eliminating the need for additional sensors—has not been systematically evaluated. This study aims to: (1) compare the predictive value of EDA versus ANI for nociception detection using machine learning approaches, (2) determine whether HRV can substitute for direct EDA measurement, (3) identify distinct autonomic response phenotypes among surgical patients how common anesthetic drugs affect both EDA and ANI by dosing.	Study Population: We analyzed continuous physiological recordings from 88 patients undergoing surgery, comprising over 16,000 5-second observation windows with synchronized HRV, EDA, and ANI measurements. Feature Extraction: HRV features included 16 time and frequency domain metrics (mean HR, SDNN, LF/HF ratio, HF power, etc.) plus their derivatives. EDA features encompassed 14 metrics and their derivatives. Nociception labels were derived from documented clinical events including surgical incision and procedural stimuli. Classification Models: We compared three modeling approaches: Logistic Regression, Random Forest, and Transformer neural networks across seven feature combinations (EDA alone, ANI alone, HRV alone, and their combinations). Performance was evaluated using area under the ROC curve (AUC) with patient-level cross-validation. Autonomic Phenotyping: We constructed composite indices for sympathetic and parasympathetic tone. K-means clustering identified patient subgroups. Drug Effect Modeling: Mixed-effects regression quantified how cumulative doses of propofol, opioids, vasopressors, and inhaled anesthetics affected ANI and EDA, controlling for surgery time, procedure duration, and patient random effects. EDA was reduced to its first principal component across all 14 features as a sensitivity analysis.	HRV Feature Correlations A. HRV vs. Skin Conductance Level B. HRV vs. ANI Feature Importance for Nociception Classification (Random Forest) A. HRV Features B. EDA Features	Predicting EDA from HRV and Drug Effects Explored Model-Adjusted Drug Effects on Autonomic Indices A. Drug Effects on ANI B. Drug Effects on EDA (PCA) Learned EDA from HRV A. HRV → EDA Prediction B. Virtual EDA for Nociception	EDA and ANI provide differing views of nociception. Despite both reflecting autonomic function, EDA and ANI show limited ability to predict each other. HRV features as expected correlate positively with ANI (HF norm: $r = 0.26$) but negatively with EDA (HR variability: $r = -0.06$). Even with deep learning, HRV-to-EDA prediction achieves only $r = 0.35$ and fails to improve nociception detection when added to ANI (AUC: $0.72 \rightarrow 0.73$). For nociception classification, both EDA and ANI contribute predictive value. Mean HR (25.5%) and skin conductance level (21.0%) emerged as top features. With Transformer models, EDA alone achieved AUC = 0.73 and ANI achieved 0.72; combining all features yielded AUC = 0.74. Importantly, modeling patients along both sympathetic (z_S) and parasympathetic (z_P) axes revealed distinct phenotypes (Fig. 7): high responders ($n=19$, 22%) showed pronounced parasympathetic withdrawal to nociception, while low responders ($n=69$, 78%) exhibited minimal autonomic change. Drug dosing systematically affects both indices. Regression revealed that anesthetic drugs differentially influence ANI and EDA readings. Opioids increased ANI ($\beta = +0.045$, $p < 0.001$) while decreasing EDA ($\beta = -0.081$, $p < 0.001$) as expected.

Model Performance Across Logistic Regression, RSF, and Transformer		Clustering	Discussion																																	
Nociception Detection: Feature Combinations <table border="1"><thead><tr><th>Feature Combination</th><th>Logistic Regression</th><th>Random Forest</th><th>Transformer</th></tr></thead><tbody><tr><td>EDA</td><td>0.61</td><td>0.68</td><td>0.73</td></tr><tr><td>ANI</td><td>0.50</td><td>0.52</td><td>0.72</td></tr><tr><td>HRV</td><td>0.59</td><td>0.60</td><td>0.70</td></tr><tr><td>EDA + ANI</td><td>0.60</td><td>0.68</td><td>0.73</td></tr><tr><td>EDA + HRV</td><td>0.63</td><td>0.69</td><td>0.72</td></tr><tr><td>ANI + HRV</td><td>0.58</td><td>0.60</td><td>0.72</td></tr><tr><td>EDA + ANI + HRV</td><td>0.62</td><td>0.68</td><td>0.74</td></tr></tbody></table>		Feature Combination	Logistic Regression	Random Forest	Transformer	EDA	0.61	0.68	0.73	ANI	0.50	0.52	0.72	HRV	0.59	0.60	0.70	EDA + ANI	0.60	0.68	0.73	EDA + HRV	0.63	0.69	0.72	ANI + HRV	0.58	0.60	0.72	EDA + ANI + HRV	0.62	0.68	0.74	HF_n (ANI Surrogate from Raw ECG) vs. ICU Admission Risk  Note: Dose-response relationship modeled using restricted cubic splines, adjusted for age, sex, BMI, ASA status, emergency surgery, and case duration. Blue line: adjusted risk with 95% CI (shaded); red points: observed rates with SE bars. The U-shaped curve shows minimum risk at HF_n 50.3%.	Autonomic Phenotypes: Physiological Index Response to Nociception A. Patient Clusters  B. High Responders  C. Low Responders 	Our findings demonstrate that EDA and ANI provide complementary rather than redundant information for nociception monitoring. Their limited mutual predictability, even with deep learning, likely reflects their representation in different autonomic branches: ANI from parasympathetic HRV modulation, EDA from sympathetic sweat gland innervation. Together, they possibly enable patient characterization along both axes of autonomic function. The identification of distinct autonomic phenotypes has clinical implications. Most patients (78%) showed blunted responses to nociception, potentially explaining inconsistent ANI performance in prior studies. Prospective phenotyping could identify the subset of patients most likely to benefit from autonomic monitoring. For validation of EDA and ANI in our dataset, drug-specific effects produced expected results with an increase in ANI and decrease in EDA with increasing opiate dosage.
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