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Automatic Detection of General Anesthetic-States using ECG-Derived Autonomic Nervous System Features

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Abstract

Electroencephalogram (EEG)-based prediction systems are used to target anesthetic-states in patients undergoing procedures with general anesthesia (GA). These systems are not widely employed in resource-limited settings because they are cost-prohibitive. Although anesthetic-drugs induce highly-structured, oscillatory neural dynamics that make EEG-based systems a principled approach for anesthetic-state monitoring, anesthetic-drugs also significantly modulate the autonomic nervous system (ANS). Because ANS dynamics can be inferred from electrocardiogram (ECG) features such as heart rate variability, it may be possible to develop an ECG-based system to infer anesthetic-states as a low-cost and practical alternative to EEG-based anesthetic-state prediction systems. In this work, we demonstrate that an ECG-based system using ANS features can be used to discriminate between non-GA and GA states in sevoflurane, with a GA F_1 score of 0.834, [95% CI, 0.776, 0.892], and in sevoflurane-plus-ketamine, with a GA F_1 score of 0.880 [0.815, 0.954]. With further refinement, ECG-based anesthetic-state systems could be developed as a fully automated system for anesthetic-state monitoring in resource-limited settings.

I. Introduction

General anesthesia (GA) is a reversible drug-induced state consisting of unconsciousness, amnesia, anti-nociception, and immobility, with the maintenance of physiological stability [1]. Anesthesiologists typically administer and adjust anesthetic-drugs empirically to achieve and maintain GA. This empiricism has been associated with the inadvertent overdosing and underdosing of anesthetic-drugs. Anesthetic-drug overdosing is associated with

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cardiovascular and respiratory side-effects and delayed recovery [2], while anesthetic-drug underdosing is associated with unintended intraoperative awareness and post-traumatic stress disorder [3]. Anesthetic-drugs induce highly-structured, oscillatory dynamics that make electroencephalogram (EEG)-based systems a principled approach for anesthetic-state monitoring. However, EEG-based anesthetic-state prediction systems are cost-prohibitive for routine use in resource-limited settings.

The American Society of Anesthesiologists mandates that every patient receiving anesthesia should have the electrocardiogram (ECG) continuously displayed from the beginning of anesthesia until the patient leaves the anesthetizing location. ECG monitoring is essential for assessing the adequacy of circulatory function. The ECG is routinely used in resource-limited settings. Heart rate variability (HRV)—the variation in instantaneous heart rate around its mean—is an important quantitative marker of autonomic nervous system (ANS) activity that can be derived from the ECG. Anesthetic-drugs significantly modulate this ANS dynamic in a dose-dependent and perhaps drug-dependent manner [4, 5]. Thus, HRV and other ANS-based features, derived from the ECG may be used to develop ECG-based anesthetic-state monitoring systems.

Sevoflurane is an inhaled anesthetic vapor that is routinely administered to maintain GA in patients. The gamma-amino-butyric acid A ($GABA_A$) receptor is considered to be the principal target receptor for the anesthetic effects of sevoflurane. Conversely, the N-methyl-D-aspartate (NMDA) receptor is considered to be the principal target receptor for the anesthetic effects of ketamine—an intravenous anesthetic that is routinely administered with sevoflurane as an anesthetic-adjunct. Both $GABA_A$ and NMDA receptors are ubiquitous to brain regions mediating ANS activity [6]. For example, the nucleus of the tractus solitarius, associated with sympathetic activity, is modulated by $GABA_A$ and NMDA receptor activity. Similarly, the dorsal motor nucleus of the vagus nerve, which is associated with parasympathetic activity, is modulated by $GABA_A$ and NMDA receptor activity. Thus, in addition to acting in neural circuits to alter the level of arousal, anesthetic-drugs also significantly modulate ANS activity by acting in brain regions mediating ANS activity.

In this work, we developed an automated ECG-based anesthetic-state prediction system to discriminate between non-GA (awake, sedated) and GA states (sevoflurane, sevoflurane-*plus*-ketamine). We also hypothesized that optimizing models for drug-specificity would result in improved ability to discriminate between the two GA states. We defined drug-specific models as those which were evaluated on data similar to that within the training set. We applied the *k*-nearest-neighbor (KNN), logistic regression, and decision tree classification algorithms to ECG-derived ANS features to investigate the feasibility of developing an ECG-based system as a low-cost and practical approach for anesthetic-state monitoring. We demonstrated that an ECG-based system using ANS features could discriminate non-GA from GA states.

II. Materials and Methods

A. Subjects and Electrocardiogram Recording

The Partners Human Research Committee approved this research study that was conducted at the Massachusetts General Hospital. A total of 12 healthy volunteers were recruited for this study (7 males; 5 females). Mean weight was 69.9 kg (SD = ±11.7) and mean BMI was 24.1 kg/m^2 (± 3.01). Subject ages ranged from 20-34 years with a mean age of 25 (±4.8). We induced and allowed recovery from sevoflurane GA and the drug-class combination of sevoflurane-*plus*-ketamine GA in each of the 12 volunteers. Thus, each volunteer received both sevoflurane-induced GA and sevoflurane-*plus*-ketamine-induced GA on separate study days, ranging 2 to 7 days apart. Sevoflurane was administered via a tight-fitting face-mask. For the sevoflurane-induced GA visit, we increased the end-tidal sevoflurane concentration in a stepwise fashion from baseline (awake) to 1.1 % (sedated), 2.1 % (GA), and 2.8 % (GA). Each concentration was maintained for 15 minutes. For the sevoflurane-*plus*-ketamine-induced GA visit, after the baseline (awake) state, we increased the sevoflurane end-tidal concentration to 2.1 % (GA) and maintained it for 15 minutes. Next, we administered a bolus dose of ketamine (0.75 mg/kg) while maintaining the sevoflurane concentration for an additional 30 minutes (GA). We recorded the ECG using the Waveguard system (ANT Neuro, Netherlands) through bipolar electrodes in standard placement.

B. Data Selection and Feature Extraction

For the sevoflurane visit, we selected 5-minute ECG epochs during the awake states (pre- and post-anesthesia) and after the sevoflurane reached the desired steady-state concentrations of 1.1 %, 2.1 %, and 2.8 %. For the sevoflurane-*plus*-ketamine visit, we selected 5-minute ECG epochs during the awake states (pre- and post-anesthesia), after the sevoflurane reached a steady-state concentration of 2.1 %, and approximately 2 minutes after the ketamine dose was administered (sevoflurane-*plus*-ketamine). A board-certified anesthesiologist (O.A.) examined the EEG oscillations associated with the ECG to confirm that data associated with sevoflurane were consistent with anesthetic states. ECG *R*-wave events were analyzed using a probabilistic model of a dynamical system observed through a point process [7, 8]. We extracted previously-defined features that have been related to parasympathetic and sympathetic activity using this point process method (Table I) [8]. For example, this feature space includes HRV, which—as discussed in the introduction—is highly related to ANS dynamics. We applied a moving average with a window size of 0.5 s to each ECG-derived ANS feature.

C. Algorithm Development and Cross-Validation

We performed two separate investigations of automatic anesthetic-state detection using ECG-derived ANS features. Our drug-specific models were model a (trained and tested on sevoflurane) and model b (trained and tested on sevoflurane-*plus*-ketamine). Our cross-test model was model c (trained on sevoflurane and tested on sevoflurane-*plus*-ketamine). First, we investigated whether a commonly-used machine-learning algorithm, trained on ECG data, could discriminate between one of three *a priori* defined anesthetic-states: GA (≥2.1% sevoflurane or 2.1% sevoflurane-*plus*-ketamine), sedation (1.1% sevoflurane), and awake (pre- or post-anesthesia). We defined this as a multiclass approach. We chose the KNN classifier ($k = 6$, endowed with the city-block metric) for our algorithm. The city-block metric—also known as the ℓ^1 metric—emphasizes small component-wise differences [9]. Given a query point q, the KNN classifier finds the k points in its training set nearest to q, where distance is defined by the city-block metric. It then uses those k points' classifications to determine the most likely classification of q.

Next, we investigated whether improvements in prediction of non-GA and GA states could be made by classifying between only two *a priori* defined anesthetic-states: awake/sedated and GA. We defined this as a binary approach. We also assessed how our choice in machine learning algorithm could affect model performance. High performance across these algorithms would indicate that ANS signatures in GA are significantly different from those in awake/sedated anesthetic-states. In addition to using KNN ($k = 6$, city-block), we trained the decision tree (minimum parent size and maximum number of categories = 10) and the logistic regression. We trained and tested the same two drug-specific models (a and b) and one cross-test model (c) as before. We kept our feature set uniform across all of our models [9].

All models were trained using a leave-one-subject-out cross-validation, which ensured that models were tested on "unseen" subjects [9]. See Fig. 1 for a model schematic. The GA (either sevoflurane or sevoflurane-*plus*-ketamine) F_1 score was used as our performance metric. We defined this metric to the harmonic mean of GA specificity (true-negative rate) and GA sensitivity (true-positive rate). Therefore, for high performance, we require high precision and recall in our GA predictions We performed ANOVA testing with post-hoc comparisons for model pairs using the Tukey-Kramer Honest Significant Difference (HSD) on GA F_1 scores. We chose a significance threshold of $p \geq 0.05$.

III. Results

We first evaluated the performance of our multiclass KNN models (model 1), results displayed in Table II. The performance of a drug-specific model that was trained and tested on sevoflurane data (model 1a) was 0.686 [95% CI, 0.592, 0.780]. The performance of a drug-specific model that was trained and tested on sevoflurane-*plus*-ketamine data (model 1b) was 0.835 [0.735, 0.934]. The performance of a cross-test model that was trained on sevoflurane data but tested on sevoflurane-*plus*-ketamine data (model 1c) was 0.701 [0.569, 0.833]. Incorporating drug-specific training sets did not improve the performance in the multiclass method. Our multiclass models, on average, had lower performances in predicting the awake state than the GA state. Model 1a, 1b, and 1c detected the awake state with F_1 scores of 0.583 [0.464, 0.702], 0.792 [0.677, 0.906], and 0.604 [0.432, 0.776], respectively. While these models had high specificity in predicting the awake state, they had low sensitivity because of misclassifications between the sedated and awake states. Model 1a detected the sedated state with a F_1 score of 0.211 [0.065, 0.356]. Most sedated epochs were classified as the awake state. Models 1b and 1c did not test the sedated state.

We then evaluated the performance of our binary (awake/sedated anesthetic-state vs GA anesthetic-state) models (model 2) across three different machine learning algorithms (KNN, decision tree, and logistic regression), results displayed in Table II. We found that the logistic regression algorithm exhibited the highest performance across drug-specific and cross-test models (2a, 2b, and 2c). The performance of a drug-specific logistic regression model that was trained and tested on sevoflurane data (model 2a) was 0.834 [0.776, 0.892]. The performance of a drug-specific logistic regression model that was trained and tested on sevoflurane-*plus*-ketamine data (model 2b) was 0.880 [0.815, 0.945]. The performance of our cross-test logistic regression model that was trained on sevoflurane data but tested on sevoflurane-*plus*-ketamine data (model 2c) was 0.789 [0.687, 0.891]. Differences in these F_1 scores did not meet our threshold for statistical significance. Model 2a, 2b, and 2c detected the awake state with awake-specific F_1 scores of 0.880 [0.758, 0.945], 0.852 [0.842, 0.918], and 0.750 [0.643, 0.858], respectively using the logistic regression algorithm. Fig. 2A displays the prediction performance of model 2a and Fig. 2B displays deviations in an illustrative subject's HRV during the sevoflurane visit.

IV. Discussion

EEG-based anesthetic-state prediction systems represent a principled approach to target anesthetic-states in patients undergoing procedures with GA. This is because anesthetic-drugs induce highly-structured, oscillatory dynamics that can be monitored using EEG-based systems. However, these systems are not widely employed in resource-limited settings because they are cost-prohibitive. In this work, we found that ANS features derived from ECG data can be used to discriminate between non-GA and GA states. Fig. 2B illustrates that the HRV during sevoflurane GA is similar to the HRV during sevoflurane-*plus*-ketamine GA. Thus, ECG-derived ANS features can be used to target anesthetic states even in clinical scenarios when drug-class combinations are administered as part of a balanced anesthetic.

HRV dynamics during the awake (pre-anesthesia, post-anesthesia) and sedated states were visually similar (Fig. 2B). Misclassifications between awake and sedated states may explain our multiclass model's poor performance on these two states. Because post-anesthesia and pre-anesthesia states were assumed to be a single awake state, it is possible that most of the k nearest neighbors of a sedated epoch were post-anesthesia epochs. Thus, other separations of our classes may improve model performance. Similarities between the ANS dynamics during the awake and sedation states may account for the improved model performance found when the two states are combined into a single non-GA class, as seen in our binary models. Models incorporating ANS features derived from ECGs will need to be further refined in order to distinguish sedation states from the awake state.

Nagaraj et al. demonstrated the feasibility of using ECG-derived features to distinguish between different levels of sedation in mechanically ventilated intensive care unit patients in two separate studies [11, 12]. This algorithm performed well (AUC = 0.75) despite the use of various drugs in critically ill patients. Our results demonstrating similarities in the performance of drug-specific and cross-test models are consistent with the findings of Nagaraj et al. that anesthetic-states can be inferred from ECG dynamics. This suggests that ECG-based anesthetic-state prediction systems may be developed as a low-cost and computationally-efficient alternative to EEG-based anesthetic-state prediction systems.

Limitations of our study include sample size, lack of acute or chronic use of ANS-modulating medications (i.e., beta-blockers), lack of pain stimuli, and lack of hemodynamic changes related to acute blood loss or volume shifts. Thus, future studies in various clinical settings are necessary to improve the generalizability of our study. We demonstrate how an ECG-based method for anesthetic-state monitoring may be feasible using a limited set of features. However, model performance—particularly in distinguishing awake from low levels of sedation—can likely be improved with a more expansive feature set or with feature independent machine learning models.

V. Conclusion

We conclude that an automated, ECG-based, anesthetic-state prediction tool using ANS features can be implemented to distinguish GA states from non-GA states. With further refinements, our model could be developed into an automated low-cost anesthetic-state prediction system.

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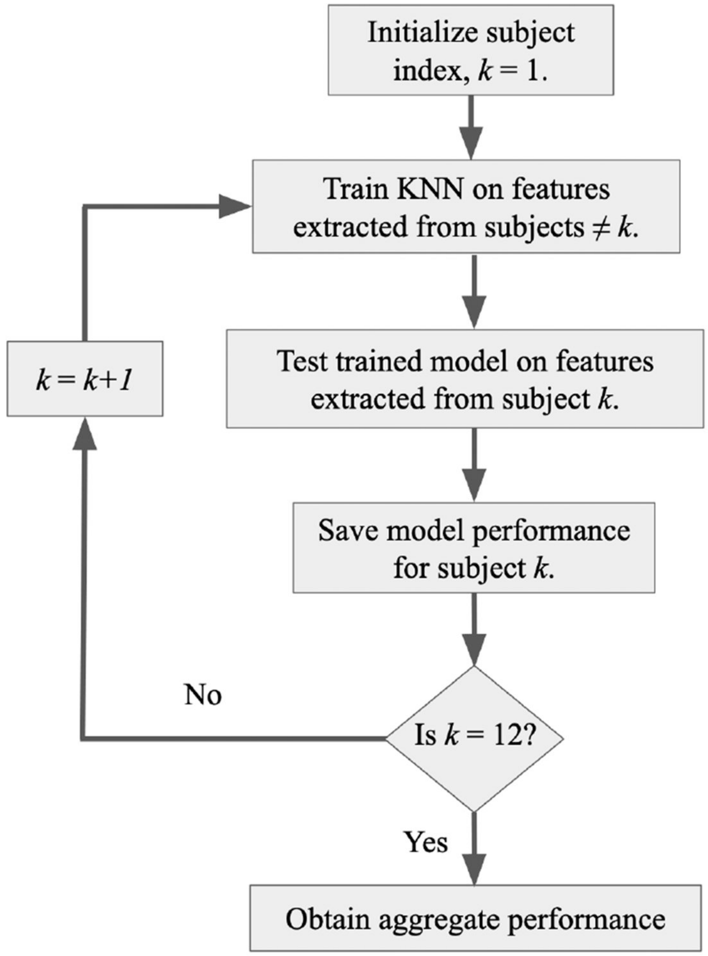

Figure 1.
Schematic of the leave-one-subject-out approach [9]

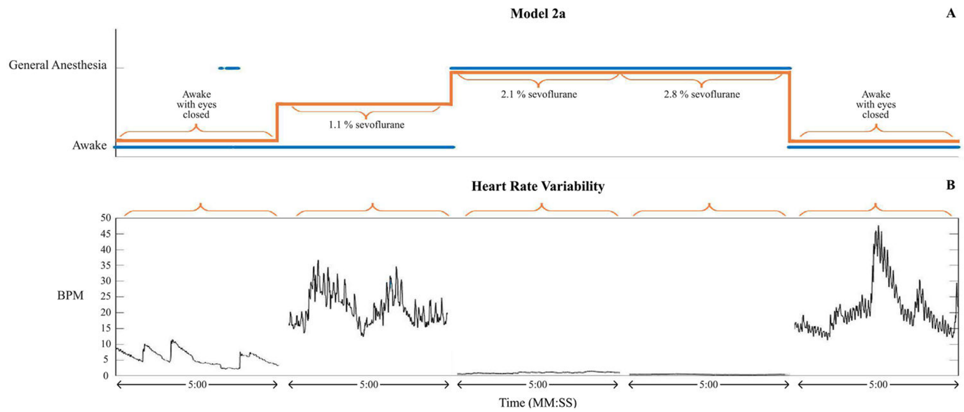

Figure 2.

Performance of model 2a (drug-specific) when testing on sevoflurane in an illustrative subject: (A, B) Predictions of model 2a (top panel) and HRV (bottom panel). Low levels of sevoflurane are associated with an increase in HRV. Orange lines represent true anesthetic-state classes and blue dots represent the class predictions for each 4-second epoch.

Table I.

Feature set

Domain	Features
Spectral	Power in very-low frequency band (0.01-0.04 Hz) Power in low frequency band (0.04-0.17 Hz) Power in high frequency band (0.17-0.38 Hz) Total power Sympathovagal balance
Time	Mean heart rate Mean R-R interval Heart rate variability R-R interval variability

Table II.

Model performance

Model	Training Data	Testing Data	Multiclass KNN on GA [CI] [iii]	Binary LR [ii] on GA [CI [iii]	Binary KNN on GA [CI] [iii]	Binary Decision Tree on GA [CI] [iii]
a	Sevoflurane	Sevoflurane	0.686 [0.591, 0.778]	0.834 [0.776, 0.892]	0.685 [0.591, 0.778]	0.784 [0.692, 0.875]
b	Sevo + Ket [i]	Sevo + Ket [i]	0.835 [0.729, 0.924]	0.880 [0.815, 0.945]	0.826 [0.729, 0.924]	0.682 [0.661,0.868]
c	Sevoflurane	Sevo + Ket [i]	0.701 [0.569, 0.832]	0.789 [0.687, 0.891]	0.701 [0.569, 0.832]	0.701 [0.536, 0.865]

i. Sevoflurane-*plus*-ketamine.

ii. Logistic Regression.

iii. 95% confidence interval.