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ORIGINAL RESEARCH **PERIOPERATIVE MEDICINE**

Heart rate variation is the clinical sign associated with the deepest plane of anesthesia during induction: the novel finding and its clinical implications

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ABSTRACT

Background: Premature airway manipulation during induction can lead to adverse patient outcomes. However, there is currently no standardized clinical sign to assess adequate anesthesia depth during induction. With the goal of increasing patient safety during induction, we aim to correlate different clinical signs during induction with the depth of anesthesia using the bispectral index (BIS) monitor and determine the physical metrics corresponding to the deepest plane of anesthesia.

Methodology: This prospective study enrolled 41 subjects scheduled for surgery requiring propofol for induction. A BIS monitor was used for standardized monitoring of anesthesia depth during the induction process. We documented the BIS value and occurrence time of the observed physical metrics: (1) loss of eyelash reflex, (2) loss of response to verbal stimuli, (3) loss of muscle tone, (4) loss of end tidal carbon dioxide ($EtCO_2$) or apnea, and (5) transient heart rate variations.

Results: Apnea, change in heart rate from baseline, and heart rate return to baseline are signs during induction associated with both lower BIS values and later occurrence when compared to other clinical signs such as loss of eyelash reflex, verbal response, and muscle tone ($P < 0.001$).

Conclusion: Physical signs such as loss of eyelash reflex, verbal response, and muscle tone during induction are associated to lighter planes of anesthesia. A safer and deeper plane of anesthesia occurs later. Relying on these physical signs for assessment of laryngeal mask airway insertion may increase the risk of stimulating the patient's airway prematurely, which can lead to adverse patient outcomes.

Abbreviations: $EtCO_2$ - End tidal carbon dioxide; BIS - Bispectral index; EEG - electroencephalogram; EKG - electrocardiogram

Key words: Depth of Anesthesia; Patient Safety; Heart rate variation; Induction

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1. INTRODUCTION

One of the most critical periods prior to surgery occurs during the induction of anesthesia. The increased risk can be attributed to the patient's level of consciousness while descending through stage two of anesthesia, described by Guedel as the period of time characterized by a state of "unconscious excitement" when reflexes such as coughing, laryngospasm, bronchospasm and vomiting are still intact.[1] Stimulating the airway during this brief yet sensitive period increases the risk of these adverse events and should be avoided. It is therefore crucial for anesthetists to be able to gauge the patient's depth of anesthesia during induction.[1]

For over a century, investigators have attempted to observe physical signs of the patient, such as eye movement, as measures of depth of anesthesia during induction. More recent clinical investigations have used loss of eyelash reflex, loss of response to verbal stimuli and loss of muscle tone to gauge depth of anesthesia during induction.[2-4] Apnea is another sign that is used to indicate depth of anesthesia.[1] Until the advent of brain wave monitoring technologies such as electroencephalograms (EEG) and Bispectral index (BIS®; Aspect Medical Systems, Inc., Newton, MA), these physical signs could not be correlated to a standardized monitor of depth of anesthesia for accurate quantification.[5] Despite extensive research on the correlation of BIS and EEG during ether and intravenous induction,[6–8] there are few prospective studies that attempt to correlate the aforementioned physical signs with real time BIS values to determine which sign corresponds to the deepest plane of anesthesia. Another observation during the peri-induction period is the heart rate changes predictably after induction with bolus doses of propofol.

This study focused on observing changes in five physical metrics during induction of anesthesia with propofol: (1) loss of eyelash reflex, (2) loss of response to verbal stimuli, (3) loss of muscle tone, (4) loss of end tidal carbon dioxide ($EtCO_2$) or apnea, and (5) transient heart rate variations. We aim to determine the metric that best correlates to the deepest plane of anesthesia to guide decision making during induction. Furthermore, we investigated distinct time points corresponding to each metric as patients descend to the appropriate surgical plane of anesthesia.

2. METHODOLOGY

2.1. Study population

This study was approved by the University of California Irvine (UCI) Institutional Review Board. The protocol was carried out at the UCI Medical Center in Orange, CA during the approval period of September 2015 to September 2016. Subjects eligible for the study were 18 to 70 y old, American Society of Anesthesiologists (ASA) physical status of 1 or 2 and scheduled for surgery requiring propofol administration for induction of anesthesia. Per the approved exclusion criteria, we did not recruit pregnant women or subjects less than 18 y of age.

2.2. Research Procedures

After the written informed consent was finalized, a BIS monitor was set up in the assigned operating room (OR) and synced with the time (hh:mm:ss) on the Anesthesia machine. Once arrived in the OR, the subject's forehead was cleaned with an alcohol swab prior to disposable BIS sensor placement. The research procedures were initiated during anesthesia timeout with establishment of a baseline heart rate (HR) value and ceased approximately one minute after propofol administration. Once the BIS monitor completed a system checkout and provided a baseline value, the device was programmed to collect the continuous BIS values via the rear USB port using a thumb drive.

Induction was performed in each patient with lidocaine 50 mg IV bolus, followed by administration of bolus dose of propofol (2 mg /kg IV). A member of the research team recorded the time of administration of induction medications and observed the following physical signs during the induction period prior to administration of neuromuscular blockade: (1) loss of eyelash reflex, (2) loss of response to verbal stimuli, (3) loss of muscle tone, (4) apnea as observed on $EtCO_2$ tracing, and (5) transient heart rate variations e.g. change in heart rate reaching maximum delta from baseline and its return to baseline. Prior to induction, the subject was routinely prompted with verbal cues and tested for eyelid reflex (1) & (2). Meanwhile, each subject was asked to hold a 500 ml saline bag for as long as possible. The moment the bag dropped was defined as the time at which the subject lost muscle tone (3). Apnea was monitored physically by observing cessation of chest movements, and was confirmed with accompanying apnea recorded on $EtCO_2$ monitor (4). The transient heart rate variations were captured in real time observing the EKG monitor and, was reconciled with electrocardiogram (EKG) rhythm strip which was continuously printed all through the peri-induction phase.[5] A stopwatch was used to time the overall length

Table 1. Baseline characteristics (n = 27)

Variables	Median [25th, 75th]
Age	46 [39, 56]
Female	19
Male	8
Height (cm)	165 [160, 172]
Weight (kg)	84 [63, 94]
Midazolam (mg)	2 [2, 2]
Induction Medications	
Fentanyl (µg)	100 [87.5, 100]
Lidocaine (mg)	50 [50, 70]
Propofol (mg)	150 [120, 150]
Paralytic (mg)	50 [8.0, 80]

of the research procedures and mark the instances ("split times") when the induction medications were administered and the listed metrics occurred. After research endpoints were completed, the BIS sensor/monitor was left to be used by the anesthesia provider at their discretion for the duration of the case.

Table 2: Median Distributions of BIS values and Times

Variable	Median BIS [25th, 75th]	Median Time (s) [25th, 75th]
Loss of eyelash reflex	86.6 [82.2, 92.0]	34.0 [26.0, 45.0]
Loss of verbal response	85.7 [82.3, 92.0]	34.0 [22.0, 45.0]
Loss of muscle tone	88.5 [82.3, 91.7]	34.0 [25.0, 46.0]
Apnea	80.0 [56.5, 85.5]	48.0 [29.0, 56.0]
∆ Heart rate	84.4 [48.8, 90.6]	44.0 [33.5, 53.5]
Return to baseline heart rate	37.5 [31.6, 50.2]	63.0 [54.0, 81.5]

Variables are presented as median [Q1, Q3]. Return to baseline heart rate was associated has a significantly lower median BIS value compared to all other variables. Median split time was also much later for return to baseline heart rate.

2.3. Data Analysis

All data from the BIS device was exported using the rear USB port as a text (ASCII) file, consolidated for analysis. Non-parametric tests – Friedman ($P < 0.0001$) and Wilcoxon-Mann-Whitney test – were used to compare the differences between each metric, Significance was defined as a p-value less than 0.01 for more conservative yet robust results by reducing the risk of type I errors. We first tested the exported BIS values for each set of variables. For example, the BIS value when the subject demonstrated loss of eyelash reflex (B_EL) were compared to the BIS value when the subject demonstrated loss of verbal response (B_VR). The split times from start of data collection were also compared for each set of variables. All analysis and nonparametric testing were performed using commercially available statistical software (SPSS).

Table 3: Study Metrics Coded for Analysis

Observed Metrics	BIS	Split Time
Loss of Eyelash Reflex	B_EL	T_EL
Loss of Verbal Response	B_VR	T_VR
Loss of Muscle Tone	B_MT	T_MT
Apnea	B_AP	T_AP
Maximum Delta Heart Rate	B_dHR	T_dHR
Back to Baseline Heart Rate	B_HR	T_HR

3. RESULTS

In total, 41 patients consented for the study, 14 subjects were excluded due to incomplete data collection during the study period. 27 subjects were ultimately included for analysis as outlined in Table 1. Approximately half (n = 13) demonstrated transient heart variations while the remaining (n = 14) subjects' heart rates were stable during the research procedures. Table 2 illustrates the calculated median distributions of the BIS values and split times at which the observed physiological signs occurred. There were no adverse events during the research period for any of the enrolled subjects. A summary of the coded metrics used for analysis are listed in Table 3.

Three physiological signs, apnea (B_AP), maximum change in heart rate from baseline (B_dHR), and heart rate return to baseline (B_HR) that exhibited significantly ($P < 0.01$) lower BIS values when compared to the BIS values of loss of eyelash reflex (B_EL), verbal response (B_VR), and muscle tone (B_MT), summarized in Table 4. The median BIS value (80) in which apnea (B_AP) occurred was significantly lower than loss of eyelash reflex (B_EL) ($P < 0.001$), verbal response (B_VR) ($P < 0.001$), and muscle tone (B_MT) ($P < 0.001$). Likewise, the median BIS value (37.5) in which maximum change in heart rate from baseline (B_dHR) occurred was significantly lower than loss of eyelash reflex (B_EL) ($P < 0.001$), verbal response (B_VR) ($P < 0.002$), and muscle tone (B_MT) ($P <$

Table 4: BIS Value associated with the occurrence of different clinical signs

Coded Metrics	B_EL	B_VR	B_MT	B_AP	B_dHR	B_HR
B_EL	--	0.313	0.367	0.0001*	0.001*	0.001*
B_VR	--	--	0.799	0.0001*	0.002*	0.001*
B_MT	--	--	--	0.0001*	0.003*	0.001*
B_AP	--	--	--	--	0.989	0.005*
B_dHR	--	--	--	--	--	0.003*
B_HR	--	--	--	--	--	--

*Comparison using Wilcoxon-Mann-Whitney (*p < 0.01). Apnea, maximum delta heart rate, and heart rate return to baseline were associated with significantly lower BIS value compared to loss of eyelash reflex, loss of verbal response, and loss of muscle tone.*

Table 5: Split Time of different clinical signs

Coded Metrics	T_EL	T_VR	T_MT	T_AP	T_dHR	T_HR
T_EL	--	0.098	0.44	0.0001*	0.002*	0.001*
T_VR	--	--	0.091	0.0001*	0.001*	0.001*
T_MT	--	--	--	0.0001*	0.004*	0.001*
T_AP	--	--	--	--	0.914	0.001*
T_dHR	--	--	--	--	--	0.001*
T_HR	--	--	--	--	--	--

*Comparison using Wilcoxon-Mann-Whitney (*p < 0.01). Apnea, maximum delta heart rate, and heart rate return to baseline were associated with significantly later split time compared to loss of eyelash reflex, loss of verbal response, and loss of muscle tone.*

0.003), but did not differ significantly from B_AP. The last significant physiological sign, maximum change in heart rate from baseline (B_dHR), exhibited a median BIS value of 80.4. This BIS value was significantly lower compared to all other studied clinical signs, including loss of eyelash reflex (B_EL) ($P < 0.001$), loss of verbal response (B_VR) ($P < 0.001$), loss of muscle tone (B_MT) ($P < 0.001$), maximum change in heart rate from baseline (B_dHR) ($P < 0.003$) and apnea (B_AP) ($P < 0.005$).

Similar to the previously mentioned lower BIS values, the permutations listed in Table 5 demonstrate that the same cluster of physiological signs that occurred significantly later: apnea (T_AP), maximum change in heart rate from baseline (T_dHR), and heart rate return to baseline (T_HR) when compared to loss of eyelash reflex (B_EL), verbal response (B_VR), and muscle tone (B_MT). Apnea (T_AP), occurred after a median time of 48 s, which was significantly later than loss of eyelash reflex (T_EL) ($P < 0.002$), verbal response (T_VR) ($P < 0.001$), and muscle tone (T_MT) ($P < 0.004$). Similarly, maximum change in heart rate from baseline (T_dHR) occurred after a median time of 63s, which was significantly later than loss of eyelash reflex (T_EL) ($P < 0.002$), verbal response (T_VR) ($P < 0.001$), and muscle tone (T_MT) ($P < 0.004$). Heart rate return to baseline (T_HR) occurred after a median time of 44 s, which was significantly later all other clinical signs including loss of eyelash reflex (T_EL) ($P < 0.001$), verbal response (T_VR) ($P < 0.001$), muscle tone (T_MT) ($P < 0.001$), maximum change in heart rate from baseline (T_dHR) ($P < 0.001$), and apnea (T_AP) ($P < 0.001$).

4. DISCUSSION

Loss of verbal contact and eyelash reflex are commonly used to estimate depth of anesthesia during induction. Based on our results, however, relying on these signs toassess adequate depth may not be ideal for the safety of patients. Additionally, there are currently no standardized physical signs used to guide the appropriate timing for airway manipulation, especially during the use of supraglottic airway such as the laryngeal mask airway (LMA). Placement of LMA usually happens much earlier than the endotracheal tube, and premature attempts at airway manipulation can lead to regurgitation, vomiting, and laryngospasm, thus posing a serious risk to the safety of patients.[9] Previous studies have associated lower BIS values with an increasing depth of anesthesia during propofol induction. However, few have appreciated the differential timing of clinical signs marking loss of consciousness or have compared their BIS values.

Our study found (4) apnea and (5) heart rate variation to be associated with significantly deeper plane of anesthesia compared to (1) loss of eyelash reflex, (2) loss of muscle tone, and (3) unresponsiveness to verbal cue. These results were consistent when comparing the time intervals of each metric from the beginning of induction. Loss of eyelash reflex, loss of muscle tone, and unresponsiveness to verbal cues occur earlier with no significant differences compared to each other while apnea and heart rate variation occur later.

These results indicate the optimal time of airway manipulation occurs much later than the moment eyelash reflex or verbal response is lost. For general anesthesia using LMA, this information is particularly crucial as it may lead to higher risk of adverse events if insertion occurs immediately after induction when adequate depth of anesthesia has not been reached. Prior evidence demonstrates that optimal condition of LMA insertion does not occur until approximately 60 seconds after loss of eyelash reflex.[10] It was also found that loss of eyelash reflex and responsiveness to verbal command occur before BIS value reaches the appropriate value, indicating that these signs correspond to a lighter plane of anesthesia.[11] While not included in our study, another report observed loss of response to mild prodding or shaking at similarly lighter depths, while loss of response to noxious electrical stimuli occurred at deeper depths.[12]

Among the five physical signs investigated in our study, heart rate variation and return to baseline were found to be associated with the deepest plane of anesthesia, confirming prior observations that heart rate variability ceases at the lowest EEG activity at 3 minutes postinduction.[13] Therefore, we hypothesize that the deepest plane of anesthesia during propofol induction occurs closer to the end of observed heart rate variations, at a much later time than loss of eyelash reflex and verbal response.

Heart rate variability during anesthesia induction is indicative of autonomic reflexes during induction of general anesthesia.[14–16] This spontaneous and irregular fluctuation of heart rate is the interplay between the patient's cardiac sympathetic and parasympathetic activity from induction agents, which are measured via low and high frequency oscillatory rhythms respectively. Heart rate variability is therefore closely linked to the type of induction agent used, patient hemodynamics, and comorbid conditions.[14,17–19]

Propofol is the most used induction agent and the hemodynamic effects during induction of general anesthesia have been long investigated but poorly understood. While several studies have observed an immediate decrease followed by an increase in HR during induction prior to laryngoscopy,[11,13] others reported prolonged decrease.[20,21] There remains a lack of consensus in heart rate outcomes following propofol induction, which is also likely complicated by addition of induction agents with varying hemodynamic profiles. As such, return to baseline heart rate may or may not be appreciated during the induction timeframe.

It is also important to recognize that the timing and associated anesthesia depth of these physical signs can be influenced by several factors such as different induction agents and patient physiological differences. For example, propofol has been associated with significantly longer times to lose eyelash reflex, become unresponsive to verbal commands, and reach lower BIS values compared to etomidate.[11,22] Addition of remifentanil may also have a concentration-dependent effect on anesthesia, with patients losing verbal response at lighter depths.[23] These known factors may influence BIS values but are unlikely to change our observed trends during propofol induction.

Similar to return to baseline heart rate, apnea was associated with a significantly deeper plane of anesthesia when compared to loss of eyelash reflex, verbal response, and muscle tone. This confirms previous evidence following induction with propofol that observed apnea at lower BIS values compared to those BIS values in patients who did not experience apnea, particularly near the recommended lower threshold of general anesthesia.[24] For our study, apnea was determined by the change in $EtCO_2$. It is important to acknowledge the inevitable delay in $EtCO_2$ change from when apnea occurs corresponding to diminished chest rise. While the median BIS value was similar in value to the values we observed in clinical signs associated with lighter sedation, this finding highlights how a deeper plane of anesthesia is more closely associated with the changes in $EtCO_2$ rather than the moment chest rise diminishes. Using $EtCO_2$ may be a more accurate and safer metric to monitor apnea during induction, as prior data suggests.[25, 26]

One of the main strengths of our study is having continuous monitoring in mind and understanding the inevitable delay in the displayed values on the BIS monitor. The user interface of the BIS monitor displays a single value (BIS index) based on the recordings of the four electrodes on the disposable head sensor, creating an inevitable delay. The values used in our analysis were therefore based on the continuous values recorded internally. To our understanding, this is also the first investigation correlating BIS values with the physical signs representing the depth of anesthesia.

Limitations of this study include the small sample size of subjects included for analysis and the higher proportion of females (n = 19) to males (n = 8). In an ideal study setting, a continuous heart rate monitor synced with the exported second-to-second BIS values for higher resolution data would be included. This data would provide much more granular detail with regards to accurately defining the maximum delta and subtle changes in heart rate variations. However, with second-to-second BIS values corresponding with visual appreciation of heart rate variations on the EKG monitor, our findings can be directly applied to the clinical setting. Both heart rate variation and anesthesia depth at loss of consciousness have been found to differ with induction agents.[27] Since all of our patients received the same induction agent (propofol), our findings cannot account for the differences in physiological effects of other induction agents. Limitations also exist with the accuracy of BIS in determining depth of anesthesia appropriate for induction. Additionally, although BIS has been found to be an effective method to measure the depth of anesthesia, values can vary with type of anesthetic agent used, age, and preexisting neurological impairment.[28−31]

5. LIMITATIONS

As our study was one of the first investigations into BIS guided depth of anesthesia and corresponding physical signs, large prospective studies are warranted in order to better understand its implications to a broader patient demographic and under different induction medications.

6. CONCLUSION

This study proposes that classic physical signs such as apnea and heart rate variation, particularly heart rate return to baseline, may best inform the anesthetist of adequate anesthesia depth and guide clinical judgement during induction. This allows both safer inductions with lower risk of airway manipulation related complications and confirmation of an appropriate amount of anesthetic medication used, thus reducing post-operative side effects.

7. Data availability

The numerical data generated in this study is available with the authors.

8. Conflict of Interest

The authors declare no conflict of interest. No external or internal funding was involved in the conduct of this study.

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10. Authors' Contribution

SC: Writing and editing manuscript, literature review

SS: Writing and editing manuscript, literature review

GR: Study design, editing manuscript

JR: Statistical analysis

AM: Study design

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