Most Hemodynamically Stable Method for Change From High to Low Anesthesia Flow: A Randomized Controlled Trial Comparing State Entropy, High Fresh Gas Flow for 10 Minutes, and 0.8 Ratio of End-Expired Agent Concentration to Inspired Agent Concentration

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This study was undertaken to determine the most hemodynamically stable method to low-flow anesthesia (LFA) between 10-minute administration of high fresh gas flow, 0.8 equilibration ratio (Fe/Fi), and state entropy (SE) between 40 and 60, a marker for adequate depth of anesthesia. Change from high fresh gas flow to LFA was done in 3 groups of 30 patients each: group T (time): 10 minutes; group R (ratio): Fe/Fi = 0.8, and group SE: SE = 40 to 50. A decrease in mean blood pressure or heart rate was treated with ephedrine or atropine, with study termination at more than 2 boluses of either. In group SE, no patient required ephedrine or atropine. The requirement for ephedrine was statistically higher in groups R and T than group SE. Atropine requirement was statistically higher in group R vs groups T and SE. In group R, the mean (SD) time to LFA was 43.9 (20.37) minutes, and in group SE was 151.9 (74.4) seconds. Hypotension or bradycardia did not occur when LFA was started at SE of 40 to 50 after anesthesia induction compared with LFA at 10 minutes, which caused hypotension, and Fe/Fi of 0.8, which caused hypotension and bradycardia.

Keywords: Hemodynamically stable, low flow, state entropy.

Advantages of low-flow anesthesia (LFA) are many, and thus LFA is frequently used in clinical practice. As the anesthetic gases are diluted with rebreathing in LFA, there is a discrepancy between the inspired and dialed anesthetic agent concentrations, and therefore some anesthetists prefer higher fresh gas flow (FGF). Time taken to reach end-tidal anesthetic agent concentration to provide sufficient anesthetic depth is known as the wash-in time, which should not last too long to achieve LFA because the effect of intravenous (IV) agents wears off with time.

Different methods have been proposed for performing LFA without prolonging the wash-in time, to achieve the end-tidal anesthetic alveolar concentration targeted to provide adequate depth of anesthesia. Some of the methods used clinically include an initial high FGF for 10 minutes during the wash-in period and an equilibration ratio of 0.8 between the end-expired agent concentration (Fe) and inspired agent concentration (Fi) (Fe/Fi = 0.8). However, to achieve a rapid wash-in time, if anesthetic agents (IV, inhalational, or a combination of both) are administered more than what the patient requires for adequate levels of anesthesia, then hypotension and/or bradycardia could result.

State entropy (SE) values between 40 and 60 are frequently used clinically to maintain adequate depth of anesthesia, which is mainly achieved by administration of propofol and/or inhalational agents intraoperatively. We hypothesized that, at anesthesia induction, isoflurane should be added to FGF only after the effect of propofol wanes off, reflected by SE more than 60, to avoid hypotension and bradycardia. The primary aim of the present study was to determine hypotension and/or bradycardia with 3 methods of LFA: high FGF for 10 minutes, Fe/Fi of 0.8, or SE of 40 to 60. The secondary aim of the study was to determine time to LFA.

Methods

After ethical clearance from the All India Institute of Medical Sciences Ethics Committee in New Delhi, India, adult patients were recruited for the study, and informed consent was obtained from all. Inclusion criteria were patients of ASA classification 1 to 2; age 18 to 60 years, and
body mass index less than 28 kg/m². Exclusion criteria were unwillingness to participate and uncontrolled diabetes mellitus, hypertension, or coronary artery disease.

All patients fasted for 8 hours and received ranitidine (150 mg, orally) and metoclopramide (10 mg, orally) the evening before surgery.

In the operating room, after IV access was obtained, Ringer's lactate solution was infused at a rate of 500 mL/h. The following monitors were applied: 3-lead electrocardiogram, noninvasive blood pressure (NIBP), pulse oximeter, and an Entropy Sensor (Entropy Module, Datex-Ohmeda, now GE Healthcare) to the forehead after cleaning with 70% isopropyl alcohol. The impedance for the Entropy Sensor was checked and noted before induction and was accepted when it was below 7.5 kΩ, in accordance with the manufacturer.

After preoxygenation by face mask (100% oxygen, 6 L/min), anesthesia was induced with fentanyl (3 μg/kg), followed 1 minute later by propofol (2 mg/kg) injected over 30 seconds. Neuromuscular blockade was established with IV vecuronium (0.1 mg/kg), and the trachea was intubated after 3 minutes. The endotracheal tube was connected to the anesthesia machine (Datex-Ohmeda S/5 Entropy Module), and mechanical ventilation was started to maintain the end-tidal carbon dioxide level between 35 and 40 mm Hg. The initial high FGF after endotracheal intubation was kept similar in all 3 groups: 4 L/min with oxygen and air was continued until SE was around 50, at which point 2.5% isoflurane was added. In these patients, from this point until SE was 40 or below was considered the time to LFA.

Patients were divided into 3 groups of 30 patients each as follows: group time (group T): LFA at 10 minutes; group ratio (group R): LFA at Fe/Fi of 0.8; and group SE: LFA at SE of 40 to 50.

The same make and capacity of breathing tube was used in all patients. The following parameters were recorded from the anesthesia machine monitor (Datex-Ohmeda S/5 Entropy): heart rate (HR), mean NIBP, and SE. The HR and SE were monitored continuously, whereas the NIBP was noted every minute for the first 10 minutes and thereafter every 5 minutes until the end point of the study was achieved. As mentioned, the end point was 10 minutes in group T, Fe/Fi of 0.8 in group R, and SE between 40 and 50 in group SE. The patient was not touched or disturbed during recording of the values.

Hypotension was defined as a decrease in mean blood pressure of 20% or more from the baseline value or a fall in systolic blood pressure to a value of 90 mm Hg or less, and it was treated with IV boluses of ephedrine (6 mg). Bradycardia was defined as a decrease in HR greater than 20/min from baseline and was treated with IV boluses of atropine (0.6 mg). If the patient at any point required more than 2 boluses of atropine or ephedrine, the study was terminated for that patient.

Three anesthetists were involved in the study. One anesthetist injected the induction drugs, and another anesthetist was responsible for mask ventilation and intubation. The values of HR and NIBP were visible to both. The third anesthetist monitored Fe/Fi and SE and noted the time to achieve Fe/Fi of 0.8 and SE between 40 and 50. He was blinded to the values of HR and NIBP. The study concluded when the end points were reached when high FGF was changed to low FGF and subsequent maintenance of low FGF was done according to the preference of the consultant anesthesiologist in charge.

In group SE, if SE increased above 70, IV boluses of propofol, 20 mg, were injected and noted in the records. If, after intubation, SE remained below 40, high FGF with oxygen and air was continued until SE was around 50, at which point 2.5% isoflurane was added. In these patients, from this point until SE was 40 or below was considered the time to LFA.

Boluses of atropine and ephedrine required were analyzed by the Fisher exact test. Both HR and NIBP being continuous variables measured at different times were statistically analyzed by analysis of variance, followed by a post hoc test for pairwise comparison. A P value less than .05 was considered statistically significant.

### Results

Ninety patients were entered into the study. Patients in all 3 groups were matched with respect to age, sex, and weight (Table 1).

In group SE, no patient required ephedrine or atropine

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<th>Table 1. Demographic Data of Patients</th>
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<td>Weight, kg</td>
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<th>Table 2. Requirement for Atropine and Ephedrine in All Three Groups</th>
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<td><strong>Group</strong></td>
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<td>R (ratio; n = 30)</td>
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<td>SE (state entropy; n = 30)</td>
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(Table 2). In group T, 9 patients (9/30; 30%) were given a single bolus of IV ephedrine, 6 mg, and 3 patients (3/30; 10%) were given 2 boluses of 6 mg of IV ephedrine. No patient required IV atropine. In group R, at least one bolus of IV ephedrine, 6 mg, was required in 8 patients (8/30; 27%), 3 of whom required 2 boluses. In 2 patients, a single dose of IV atropine, 0.6 mg, was given without ephedrine. The requirement for ephedrine was significantly higher in groups R and T compared with group SE (P < .05). The requirement for atropine was significantly higher in group R compared with groups T and SE (P < .05; see Table 2). In group R, the HR and mean NIBP reached lower values compared with the other groups (Figures 1 and 2).

In group R, the mean (SD) time to LFA was 43.9 (20.37) minutes. In 3 patients, the Fe/Fi of 0.8 was not achieved until the end of the surgery, and in those 3 patients, the study was abandoned because they required more than 2 boluses of ephedrine, 6 mg. In 4 patients, the Fe/Fi ratio was achieved in less than 30 minutes, whereas in 20 patients the ratio was attained in more than 30 minutes (Figure 3).

In group SE, the mean (SD) time to LFA was 151.9 (74.4) seconds. In group SE, in the peri-intubation period, SE remained more than 70 in 3 patients (3/30; 10%), which decreased to below 60 with a single bolus of IV propofol, 20 mg. The SE remained below 40 in 4 patients (4/30; 13%) after endotracheal intubation and increased to 40 to 50 at 45, 140, 170, and 180 seconds.

Mean end-expired concentration of isoflurane at the end points in the 3 groups (ie, at 10 minutes, at SE of 40 to 50, and at Fe/Fi of 0.8 in group T, group SE, and group R) was 1.35, 1.04 and 1.33, respectively.

**Discussion**

After endotracheal intubation, LFA initiated at SE of 40 to 50 caused no hypotension or bradycardia compared with LFA at 10 minutes, which caused hypotension, and Fe/Fi of 0.8, which caused hypotension and bradycardia. The time required to change from high to low FGF at SE of 40 to 50 was 151.9 seconds.

The wash-in time for LFA is described differently in various studies. Various authors have described a wash-in time of 10 minutes; however, the composition of anesthetic gases is not similar in all studies. Barcin et al described an FGF rate of 4.4 L/min with 1.5% isoflurane administered for 10 minutes. Baum described an
initial FGF rate of 4 L/min with 2.5% isoflurane for 10 minutes, after which the FGF rate was reduced to 0.5 L/min. Virtue used an initial FGF rate of 3 L/min with nitrous oxide and oxygen for 15 to 20 minutes. Coetzee et al. after intubation, set the FGF at 4 L/min of nitrous oxide and 2 L/min of oxygen with isoflurane, desflurane, and sevoflurane, and when Fe/Fi reached 0.8, FGF was reduced to 250 mL/min of nitrous oxide and 250 mL/min of oxygen. With isoflurane, Fe/Fi reached 0.8 at 19.7 minutes in their study. Lee et al. set the initial gas flows at 6 L/min with inhalational agents, and when Fe/Fi reached 0.8, the gas flows were reduced to 500 mL/min with 50% nitrous oxide and 50% oxygen. A long time to achieve Fe/Fi of 0.8 with isoflurane is attributed to its high solubility. To the best of our knowledge, none of these studies described the hemodynamic changes until Fe/Fi of 0.8 was achieved. In the present study, the addition of isoflurane to high FGF until the Fe/Fi of 0.8 was achieved resulted in hypotension and bradycardia.

Monitors such as the bispectral index (BIS, Medtronic), SE (GE Healthcare), and Narcotrend (Nonin) are useful in the assessment of depth of anesthesia during the induction phase. The Entropy Module calculates 2 different spectral entropy indicators; SE reflects the electroencephalogram (EEG)-dominant part of the spectrum, and response entropy includes electromyography along with EEG-dominant components of the spectrum. Values of SE 40 to 60 denote adequacy of hypnosis and correspond to the BIS.

For anesthesia, the reliable monitoring of anesthetic drug effects on the brain is a clinical concern for anesthesiologists. The central nervous system is the main target of anesthetic drugs. Originated in the central nervous system, the EEG reflects the neuronal activities and has been widely used as a surrogate parameter to quantify the anesthetic drug effect. It has been suggested that before intubation BIS values around 50 should be achieved because there is a mean increase in BIS values of 8 points at intubation, which would avoid the critical BIS value for awareness at values more than 60. Thus, in the present study a value of 40 to 60 before intubation in group ratio was aimed for.

Propofol is used commonly for IV induction of anesthesia and is associated with dose-dependent decrease in blood pressure and apnea compared with other IV induction agents. Propofol has an initial distribution half-life of 2 to 8 minutes, which varies with the patient’s age, weight, and systemic morbidity. In the present study, SE remained below 40 in 13% of patients even after intubation, which is concerning because the addition of isoflurane when SE is already less than 40 could result in hypotension due to vasodilation caused by both propofol and isoflurane. In 10% of patients, SE was more than 60 after induction with propofol, fentanyl and vecuronium, which could result in awareness. Thus, it is essential that at induction SE be monitored to guide administration of propofol boluses and/or isoflurane for LFA.

From the present study, we are unable to determine if a time of 156 seconds to LFA truly reflects brain equilibrium of isoflurane; however, we can safely say that the synergistic effect of anesthetic drugs (isoflurane, propofol, and fentanyl) is present in sufficient amounts in the “fatty” brain to produce adequate anesthesia as reflected by SE. Nevertheless, we must remember that an anesthetic agent does not “target” the brain, but because brain is mostly fatty, the agent’s effect on the brain is manifested first. Extra time of anesthetic drugs would result in these drugs dissolving in other tissues of heart and vasomotor center, causing unwanted side effects of bradycardia and hypotension as was seen in the present study.

A limitation of the present study is the late addition of isoflurane to the breathing circuit, a concern for equilibration to occur; however, clinically in no patient did SE reach more than 60. Also, the present study used entropy as a surrogate marker of the tonicity of vessels, as in previous studies. Further studies to directly monitor the vessel tonicity would be more factual.

**Conclusion**

Hypotension or bradycardia does not occur when LFA is started at SE 40 to 50 after anesthesia induction with propofol, vecuronium, fentanyl, and isoflurane, compared with LFA at 10 minutes, which causes hypotension, and Fe/Fi of 0.8, which causes hypotension and bradycardia.

**REFERENCES**

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**DISCLOSURES**

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