1-1-8 one-step sevoflurane-nitrous oxide wash-in scheme for low-flow anesthesia: simple, rapid, and predictable induction

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Abstract

Background Sevoflurane is suitable for low-flow anesthesia (LFA). LFA needs a wash-in phase. The reported sevoflurane wash-in schemes lack simplicity, target coverage, and applicability. We proposed a one-step 1-1-8 wash-in scheme for sevoflurane-nitrous oxide (N2O) LFA. The objective of our study was to identify times to achieve every alveolar concentration of sevoflurane (FAS) from 1% to 3.5%. Methods We recruited 102 adults requiring general anesthesia with endotracheal intubation and controlled ventilation. After induction and intubation, a wash-in was started using a fresh gas flow of oxygen (O2):N2O at 1:1 L·min-1 plus sevoflurane 8%. The ventilation was controlled to maintain end-tidal carbon dioxide (CO2) of 30-35 mmHg. Results The rising patterns of FAS and inspired concentration of sevoflurane (FIS) are similar and parallel. The FAS/FIS ratio increased from 0.46 to 0.72 within 260 sec. The respective times to achieve FAS of 1%, 1.5%, 2%, 2.5%, 3% and 3.5% were 1, 1.5, 2, 3, 3.5, and 4.5 min. The heart rate and blood pressure significantly increased initially then gradually decreased as FAS increased. Conclusions The 1-1-8 wash-in scheme for sevoflurane has many advantages, including simplicity, coverage, swiftness, safety, and economy. A respective FAS of 1%, 1.5%, 2%, 2.5%, 3%, and 3.5% can be expected at 1, 1.5, 2, 3, 3.5, and 4.5 min. This scheme may be applied for LFA in the situation where anesthetic gas analyzer is not available.

Background

Low-flow anesthesia (LFA; fresh gas flow (FGF) ≤ 1 L·min-1) is gaining popularity because it has many benefits, including a relatively lower cost, less environmental burden, and an increase in humidity and temperature of inspired gas, leading to improved mucociliary function of the patient [1]. Since use of low FGF leads to a long time constant, a wash-in phase using high FGF and high vaporizer concentration of volatile anesthetic (FV) is warranted to rapidly achieve the required concentration of inhalation anesthetic in the breathing system. Sevoflurane—when used with strong base-free CO2 absorbent—is suitable for use in LFA because it has low blood-gas solubility. There are a few reports regarding wash-in schemes of sevoflurane for LFA but those studies achieved only one or two targets of alveolar concentration (FA) of sevoflurane (FAS) [2-4]. We propose a simple one-step 1-1-8 wash-in scheme for sevoflurane using FGF of O2:N2O at 1:1 L·min-1 and a FV of sevoflurane (FVS) 8%, which can be used to estimate the time to achieve every FAS in daily practice.

The primary objective of the current study was to identify the time to achieve a FAS of 1%, 1.5%, 2%, 2.5%, 3%, and 3.5%. The secondary objectives were to identify the changes in heart rate and blood pressure during wash-in.

Methods

This study is reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [5].

The current study was approved by the Khon Kaen University Ethics Committee in Human Research (HE601228), and was registered with ClinicalTrials.gov (NCT03510013). The study was conducted in accordance with Declaration of Helsinki and the ICH GCP. All participants gave written informed consent before being recruited into the study.

This was a prospective descriptive study. We calculated the sample size from a pilot study on 20 patients, which identified a standard deviation of 40 sec at an FAS of 3.5%. With the total width of the expected confidence interval of 16 sec and a significance criterion of 0.05, the total number of patients required was 96. We recruited 102 patients to cover a 6% drop-out rate. The inclusion criteria were adult patients, age 18-64, with an American Society of Anesthesiologists (ASA) physical status of 1-2 undergoing elective surgery under general anesthesia at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The exclusion criteria were: patients with a BMI > 30 kg·m-2; a contraindication for N2O or succinylcholine; having pulmonary or cardiac disease; or, being pregnant.

All patients received standard intra-operative anesthetic monitoring and care. The monitoring included electrocardiogram, pulse oximetry, non-invasive blood pressure measurement, and capnography. The anesthetic machine with integrated anesthetic gas analyzer used in this study was the Dräger Primus (Dräger AG, Lübeck, Germany). We used a standard circle circuit with Litholyme as the CO2 absorbent. Heart rate and blood pressure were recorded as baseline parameters before induction of anesthesia. After pre-oxygenation for 3 min, each patient was premedicated with fentanyl 1-2 μg·kg-1, and then propofol 2 mg·kg-1 was given as the induction agent. Endotracheal intubation was facilitated with succinylcholine 1.5 mg·kg-1. After a correct endotracheal tube position was confirmed, cisatracurium 0.15 mg·kg-1 was given. The ventilation was controlled using O2:N2O at 1:1 L·min-1 and FVS of 8%. The ventilator was set as volume-control with a tidal volume of 8 mL·kg-1 and a respiratory rate of 12 min-1, which was adjusted periodically to achieve an end-tidal CO2 of 30-35 mmHg. The times to achieve a respective FAS of 1%, 1.5%, 2%, 2.5%, 3%, and 3.5% were recorded as the primary outcome. The inspired concentration (FI) of sevoflurane (FIS), heart rate, and blood pressure at each FAS were recorded as the secondary outcomes. When the FAS reached 3.5%, the FGF was reduced to 1 L·min-1 and the FVS was readjusted at the discretion of the attending anesthesiologist.

Statistical analysis

Continuous data were presented as means ± standard deviation (SD) while categorical data were presented as numbers (%). The primary outcomes were presented as means ±SD with a 95% confidence interval (CI). The secondary outcomes (i.e., heart rate and blood pressure at different time points) were compared using repeated measures analysis of variance. A $P < 0.05$ was considered to be statistically significant. All data were analysed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 102 patients were recruited from September to December 2018. The patient and clinical characteristics are shown in Table 1. The trajectories of time to achieve each FAS for all patients are

presented in Figure 1. The gradual rising pattern of FAS and FIS are similar and parallel (Figure 2). The ratio of FAS/FIS rises rapidly from 0.46 to 0.72 within 260 sec (Figure 3). The respective time to achieve a FAS of 1%, 1.5%, 2%, 2.5%, 3%, and 3.5% (in sec) with 95% CI and the approximate upper limit of the CI (in min) are presented in Table 2. A FAS of 3.5% can be achieved within 4.5 min. The heart rate and blood pressure slightly increased initially then gradually decreased as the FAS increased (Figure 4).

Discussion

Sevoflurane is a popular and widely used volatile anesthetic because it does not irritate the airway, hence it can be used as an induction agent, especially in children. Moreover, its low blood and fat solubility leads to rapid onset, easy depth of anesthesia adjustment, and early recovery [6]. Due to its high cost, however, LFA is necessary to reduce the amount needed and thereby control cost [7]. Previously, the recommended lowest FGF to be used with sevoflurane was 1 L·min-1 for exposures up to 1 h and 2 L·min-1 for exposures > 1 h because of compound A concern [8]. With the introduction of strong base-free CO2 absorbents (e.g., Amsorb Plus and Litholyme), the issue with compound A from sevoflurane has been resolved and sevoflurane can be safely used in LFA [9]. LFA, however, needs a wash-in phase to rapidly build up FAS to a therapeutic level. The wash-in can be achieved by (a) increasing FGF to reduce the time constant [10]. (b) increasing FVS to induce a concentration effect [11], or (c) integrating both methods.

A few studies have addressed the wash-in technique for sevoflurane LFA. Lindqvist and Jakobsson reported a 2-step wash-in technique to achieve a FAS of 1.2%; starting with FGF 1 L·min-1 and FVS 8% for 1 min, then reducing FGF to 1, 0.7, 0.5, and 0.3 L·min-1. They found that the respective time to achieve the target FAS was 1.8, 1.5, 2.5, and 3.6 min [4]. Horwitz and Jakobsson reported that by using a FGF of 1.0 or 0.5 L·min-1 with a FVS 6% during the wash-in, the respective time to reach 1 MAC was 6.2±1.3 and 15.2±2.4 min and up to 1.5 MAC at 7.5±2.5 and 19±4.4 min [2]. The limitation of these two schemes is that they cover only 1 or 2 FAS targets, and hence cannot be applied for other required FAS.

Jakobsson and colleagues reported a wash-in in a test-lung model with a respective FGF of 0.3 and 4 L·min-1 and a FVS of 8%. They found that the FAS reached 1 MAC (2.1%) at 547±83 and 38±6 sec, respectively [3]. Leijonhufvud and colleagues reported a wash-in in a test-lung using a respective FGF of 1, 2, 4, 4.8, 6, and 8 L·min-1 and a FVS 6% in Flow-I and Aisys anesthetic machine and found that the mean times to achieve 1 MAC was 431.3, 185.6, 66, 53.6, 53.6, and 52.6 sec for Flow-I and 262.7, 144.3, 57.7, 52.3, 57.7, and 58.3 sec for Aisys [12]. Finally, Shin and colleagues performed a wash-in study using a Primus anesthetic machine connected to a test-lung, using a FGF of 0.5, 1, and 3 L·min-1 and setting the FVS to 6%. The respective mean times to reach FAS of 4% for each FGF were 1,165, 534, and 155 sec [13]. The latter 3 studies were, however, all performed in test-lungs such that the uptake of sevoflurane by body tissues was not considered. So, they cannot infer to real clinical practice.

The current study proposed a 1-1-8 wash-in scheme for sevoflurane-nitrous oxide LFA—which can rapidly and predictably achieve every FAS (i.e., 1% to 3.5% as is used in daily practice within 4.5 min). The current wash-in scheme uses O2:N2O 1:1 L·min-1 as the carrier gases because, without contraindication, 50%

N2O provides 0.5 MAC in addition to the MAC of sevoflurane [14], hence this protocol can further save on the costs of sevoflurane.

Comparing with a similar 1-1-12 wash-in scheme for desflurane LFA which uses desflurane 12% (2 MAC) [15,16], the current 1-1-8 sevoflurane-N2O wash-in scheme uses a higher MAC (8% or 4 MAC) of sevoflurane. The reasons include (1) sevoflurane has greater blood and fat solubility than desflurane; leading to higher body tissue uptake, which results in a longer time to achieve an equivalent MAC, and (2) sevoflurane has a 3 times lower MAC value, hence we used 4 MAC of sevoflurane to augment a concentration effect.

The trajectories of the times to achieve each FAS (Figure 1) suggest that the tested wash-in scheme has acceptable intra- and inter-subject variability. The parallel rising pattern of FAS and FIS (Figure 2) shows that the wash-in scheme has enough power to drive both FAS and FIS to the desired target within 4.5 min, which is reflected in the rising FAS/FIS ratio pattern (Figure 3). The rising FA/FI ratio pattern reflects the onset of volatile anesthetic, and the more rapid the rise the shorter the onset. The FAS/FIS ratio of the 1-1-8 wash-in scheme rose to 0.72 within 260 sec, which underscores the efficacy of this scheme.

The changes in heart rate and blood pressure during the wash-in process are similar to the 1-1-12 wash-in scheme for desflurane [15-16] (i.e., slightly increasing initially then gradually decreasing as presented in Figure 4). The changes are statistically but not clinically significant.

The 1-1-8 wash-in scheme has many advantages: (a) simplicity (just a one-step setting); (b) coverage (includes every FAS target, from 1% to 3.5%, used in daily practice both in balanced anesthesia and pure inhalation anesthesia); (c) swiftness (accomplishing the desired target within 1 to 4.5 min); (d) safety (no clinically significant change in heart rate and blood pressure); and (e) economy (just 2 L·min-1 of FGF). When the target FAS is achieved, the FGF can be reduced to 1 L· min-1 and the FAS can simply be maintained by setting the FVS above the desired FAS by 50% to 60% [4,17]. The current study used Litholyme as the CO2 absorbent to guarantee the safety of sevoflurane LFA.

Most hospitals in developed countries have an anesthetic gas analyser in the operating theatre, making any wash-in scheme unnecessary during low-flow anesthesia. Many operating theatres in less developed areas, however, still lack an anesthetic gas analyser. The tested wash-in scheme may thus be applied in situations where an anesthetic gas analyzer is not available.

Limitations

Since we excluded patients with a BMI >30 kg m-2, this wash-in scheme may not be applied in this group of patients. The current study used N2O as a carrier gas, so the results may not be generalised to settings where N2O has been omitted. Further studies are required.

Conclusions

In patients requiring general anesthesia with endotracheal intubation and controlled ventilation, the 1-1-8 wash-in scheme for sevoflurane-N2O LFA yields a respective FAS of 1%, 1.5%, 2%, 2.5%, 3%, and 3.5% at 1, 1.5, 2, 3, 3.5, and 4.5 min. The technique uses a one-step setting for O2:N2O 1:1 L·min-1 with sevoflurane 8%. There were statistically but no clinically significant changes in heart rate and blood pressure during the wash-in process. This scheme may be applied for LFA in the situation where anesthetic gas analyzer is not available.

List Of Abbreviations

N2O: nitrous oxide; FAS: alveolar concentration of sevoflurane; O2: oxygen; CO2: carbon dioxide; FIS: inspired concentration of sevoflurane; FGF: fresh gas flow; FV: vaporizer concentration of volatile anesthetic; FA: alveolar concentration; FVS: vaporizer concentration of sevoflurane; ASA: American Society of Anesthesiologists; SD: standard deviation; CI: confidence interval.

Declarations

Ethics approval and consent to participate

The current study was approved by the Khon Kaen University Ethics Committee in Human Research (HE601228). All participants gave written informed consent before being recruited into the study

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and its additional file).

Competing interests

The authors have no competing interest.

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Authors' contribution

ST and TS designed the study, performed the study, performed the statistical analysis and wrote the manuscript. NV, MT, DN, and WS performed the study and collected data. All authors read and approved the final manuscript.

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References

1. Baum JA. Low-flow anesthesia: theory, practice, technical preconditions, advantages, and foreign gas accumulation. J Anesth. 1999;13:166-74.

2. Horwitz M, Jakobsson JG. Desflurane and sevoflurane use during low- and minimal-flow anesthesia at fixed vaporizer settings. Minerva Anestesiol. 2016;82:180-5. PMID: 26198766.

3. Jakobsson P, Lindgren M, Jakobsson JG. Wash-in and wash-out of sevoflurane in a test-lung model: A comparison between Aisys and FLOW-i. F1000Res. 2017;6:389.

4. Lindqvist M, Jakobsson J. Minimal flow anesthesia for short elective day case surgery; high vaporiser settings are needed but still cost-effective. Ambul Surg. 2011;17:27-9.

5. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

6. Young CJ, Apfelbaum JL. Inhalational anesthetics: desflurane and sevoflurane. J Clin Anesth. 1995;7:564-77.

7. Ryu HG, Lee JH, Lee KK, Gil NS, Kim CS, Sim SE, et al. The effect of low fresh gas flow rate on sevoflurane consumption. Korean J Anesthesiol. 2011;60:75-7.

8. Gentz BA, Malan TP, Jr. Renal toxicity with sevoflurane: a storm in a teacup? Drugs. 2001;61:2155-62.

9. Marini F, Bellugi I, Gambi D, Pacenti M, Dugheri S, Focardi L, et al. Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anesthesia: comparison of three carbon dioxide absorbers. Acta Anaesthesiol Scand. 2007;51:625-32.

10. Honemann C, Hagemann O, Doll D. Inhalational anesthesia with low fresh gas flow. Indian J Anesth. 2013;57:345-50.

11. Korman B, Mapleson WW. Concentration and second gas effects: can the accepted explanation be improved? Br J Anesth. 1997;78:618-25.

12. Leijonhufvud F, Joneby F, Jakobsson JG. The impact of fresh gas flow on wash-in, wash-out time and gas consumption for sevoflurane and desflurane, comparing two anesthesia machines, a test-lung study. F1000Res. 2017;6:1997.

13. Shin HW, Yu HN, Bae GE, Huh H, Park JY, Kim JY. The effect of fresh gas flow rate and type of anesthesia machine on time to reach target sevoflurane concentration. BMC Anesthesiol. 2017;17:10.

14. Vereecke HE, Proost JH, Heyse B, Eleveld DJ, Katoh T, Luginbuhl M, et al. Interaction between nitrous oxide, sevoflurane, and opioids: a response surface approach. Anesthesiology. 2013;118:894-902.

15. Sathitkarnmanee T, Tribuddharat S, Suttinarakorn C, Nonlhaopol D, Thananun M, Somdee W, et al. 1-1-12 one-step wash-in scheme for desflurane-nitrous oxide low-flow anesthesia: rapid and predictable induction. Biomed Res Int. 2014;2014:867504.

16. Sathitkarnmanee T, Tribuddharat S, Nonlhaopol D, Thananun M, Somdee W. 1-1-12 one-step wash-in scheme for desflurane low flow anesthesia: performance without nitrous oxide. Drug Des Devel Ther. 2015;9:977-81.

17. Hargasser S, Hipp R, Breinbauer B, Mielke L, Entholzner E, Rust M. A lower solubility recommends the use of desflurane more than isoflurane, halothane, and enflurane under low-flow conditions. J Clin Anesth. 1995;7:49-53.

Tables

Table 1 Patient and clinical characteristics

Parameter	Value
Age (years)	42.47±12.73
Weight (kg)	58.58±10.02
Height (m)	1.60±0.06
Sex	
Male	22 (21.57)
Female	80 (78.43)
ASA classification	
1	71 (69.61)
2	31 (30.39)
Systolic blood pressure (mmHg)	135.64±20.21
Diastolic blood pressure (mmHg)	80.92±10.16
Heart rate (beat/min)	80.20±14.49

Data are presented as means ±SD or numbers (%).

ASA, American Society of Anesthesiologists.

Table 2 Actual time in seconds with 95% CI and approximated upper CI limit time in minutes to achieve each FAS (n = 102)

FAS (%)	FIS (%)	Time (sec)	95%CI (sec)	Approximated upper CI limit time (min)
1	2.2	45.8±9.8	43.9-47.8	1
1.5	2.7	73.5±14.5	70.7-76.4	1.5
2	3.2	116.3±20.4	112.3-120.3	2
2.5	3.8	161.9±23.3	157.3-166.4	3
3	4.4	208.4±30.6	202.4-214.4	3.5
3.5	4.9	258.5±35.0	251.7-265.4	4.5

Data are presented as means ±SD or ranges.

FIS, inspired concentration of sevoflurane; FAS, alveolar concentration of sevoflurane; CI, confidence interval.

Figures

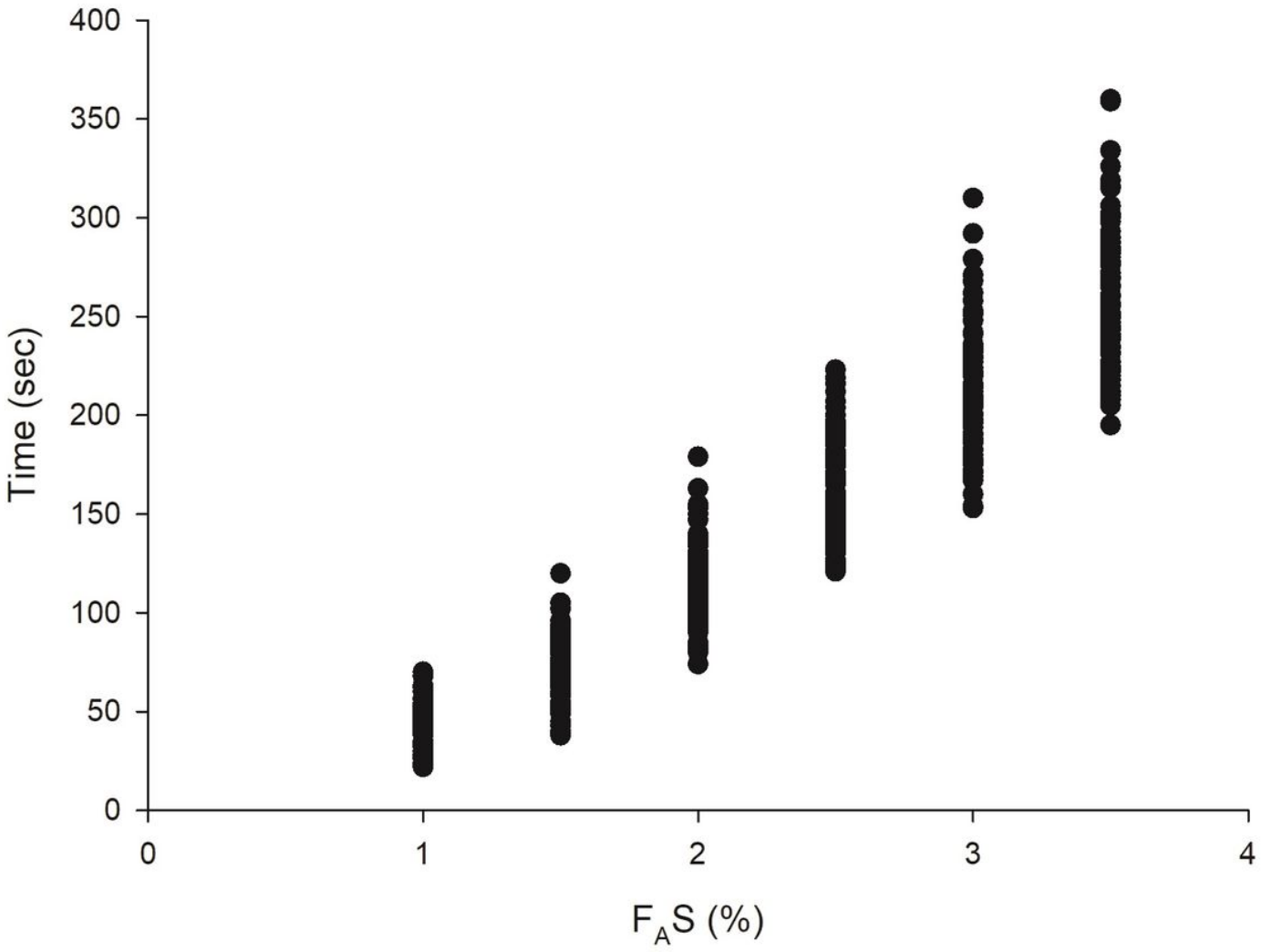

Figure 1

Trajectories of FAS vs. time to achieve each FAS during wash-in. FAS, alveolar concentration of sevoflurane.

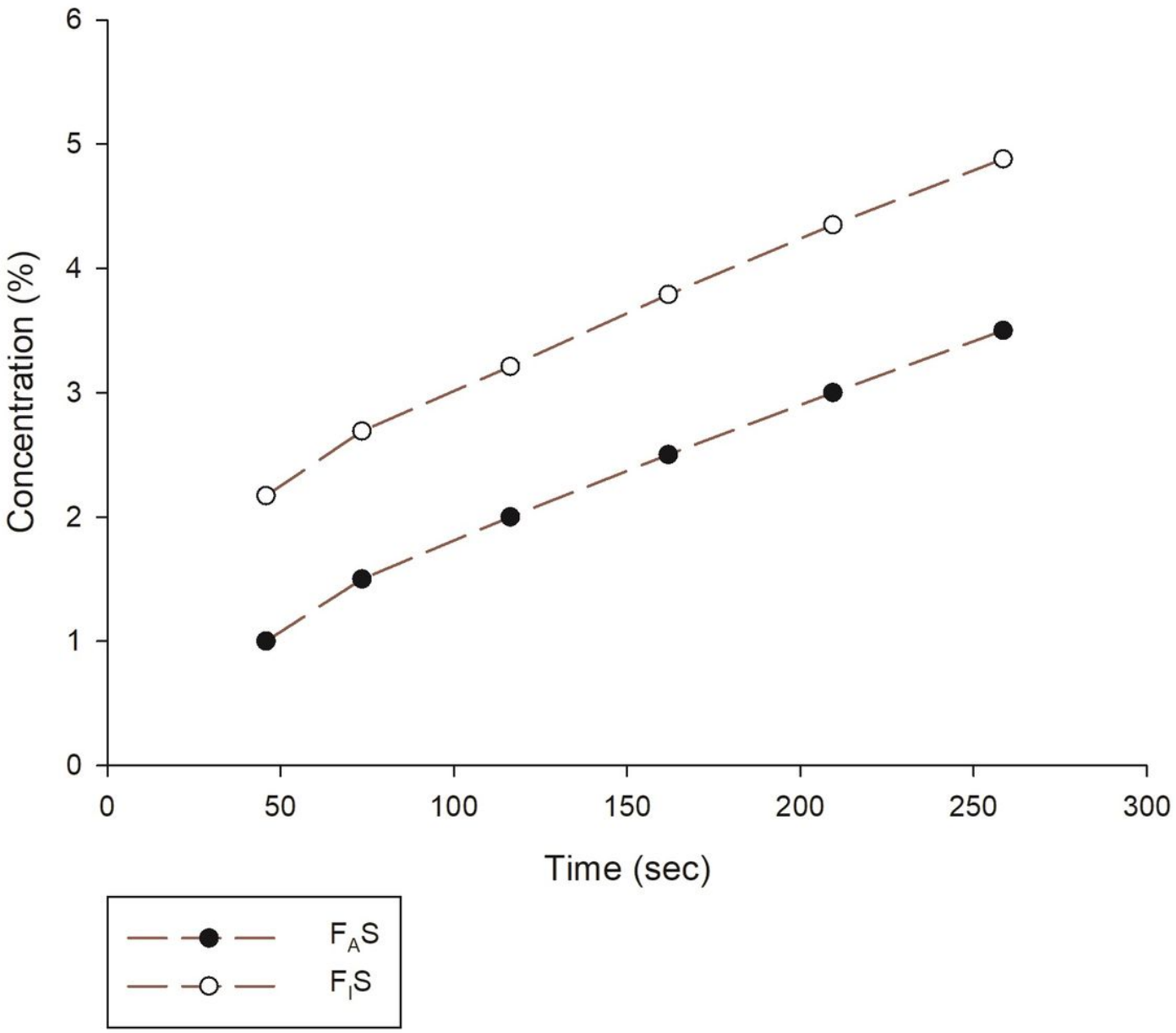

Figure 2

Rising pattern of FAS and FIS. FAS, alveolar concentration of sevoflurane; FIS, inspired concentration of sevoflurane

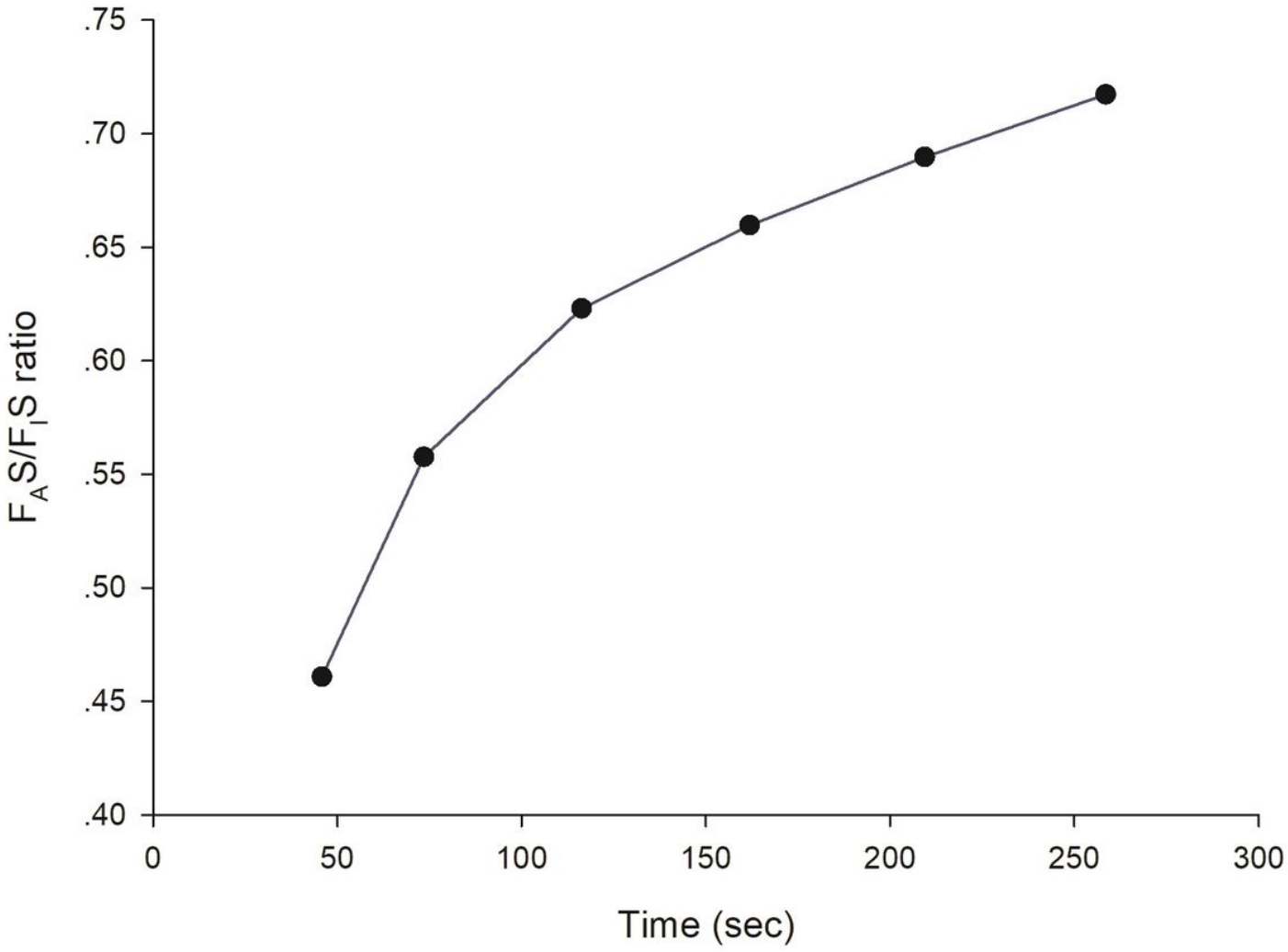

Figure 3

Rising pattern of FAS and FIS. FAS, alveolar concentration of sevoflurane; FIS, inspired concentration of sevoflurane

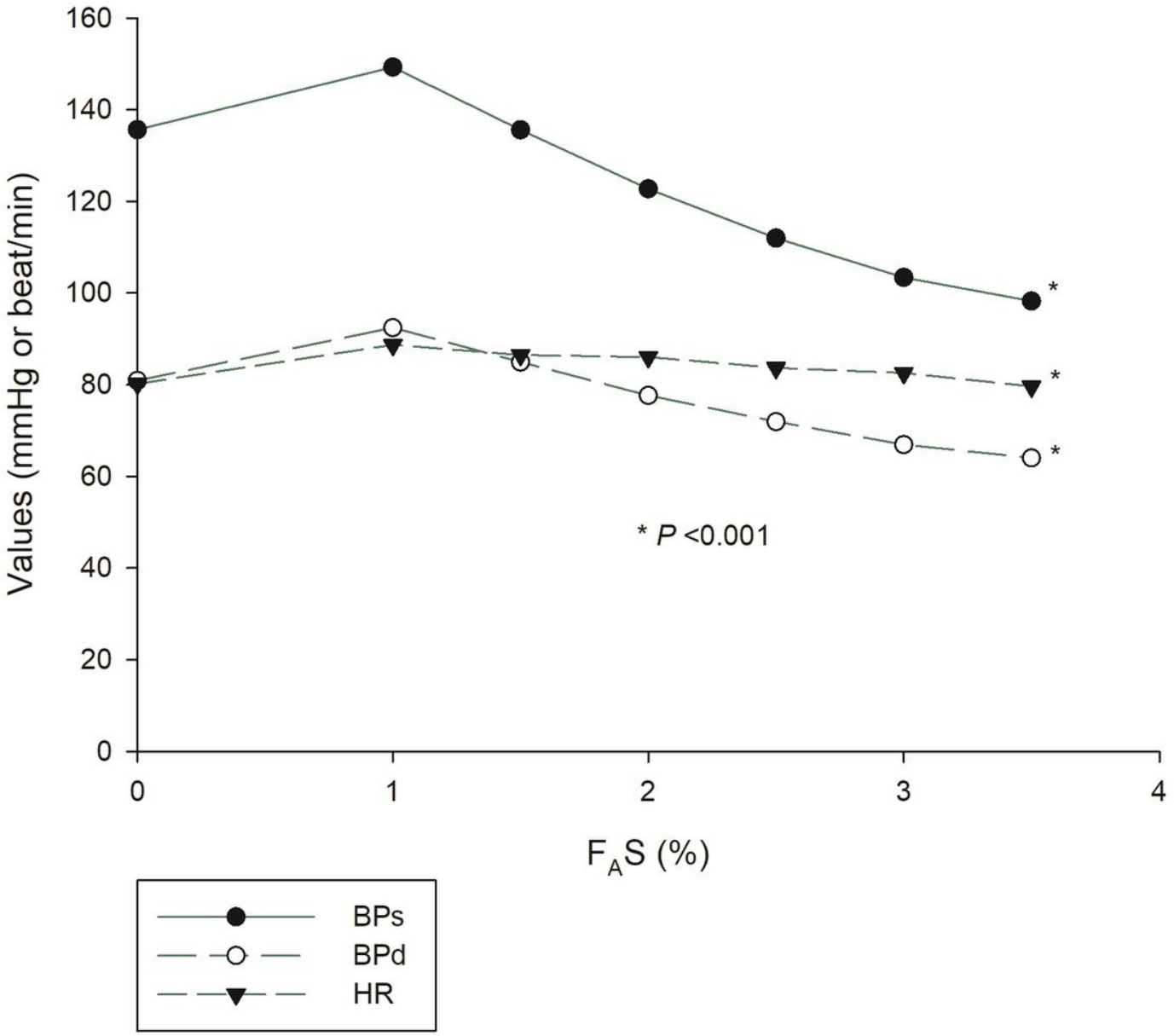

Figure 4

Pattern of changes in heart rate and blood pressure. FAS, alveolar concentration of sevoflurane; BPs, systolic blood pressure; BPd, diastolic blood pressure; HR, heart rate.

Supplementary Files

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- supplement1.xlsx
- supplement2.doc