Respiratory Depression Following Cesarean Delivery With Single-Shot Spinal With 100 µg Morphine

Hiroki Onodera CE
Nara Medical University
Mitsuru Ida (nwnh0131@yahoo.co.jp)
Nara Medical University https://orcid.org/0000-0001-5285-257X
Yusuke Naito
Nara Medical University https://orcid.org/0000-0002-1423-812X
Yuka Akasaki
Nara Medical University
Akane Kinomoto
Nara Medical University
Masahiko Kawaguchi
Nara Medical University

Research Article

Keywords: cesarean delivery, intrathecal morphine, respiratory depression, continuous monitoring

Posted Date: June 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-517792/v1

Abstract

Purpose: We aimed to evaluate the rate of cumulative bradypnea time (total bradypnea time/total monitoring time) and its related factors in these parturients.

Methods: This was a prospective observational study of women undergoing elective and non-elective cesarean delivery under single-shot spinal including 0.1 mg morphine. The Berlin Questionnaire was used to screen for sleep apnea syndrome preoperatively. Respiratory rate and oxygen saturation (SpO_2) were monitored continuously using an adhesive acoustic respiration sensor and pulse oximeter, respectively, at least 6 hours after cesarean delivery. Bradypnea was defined as a respiratory rate < 8 bpm lasting at least 25 s (sustained bradypnea) and at least 15 s (immediate bradypnea), respectively. Hypoxemia was defined as SpO_2 < 92% lasting at least 25 s (sustained hypoxemia) and at least 15 s (immediate hypoxemia) multiple regression analysis was applied to assess related factors to the rate of cumulative sustained bradypnea.

Results: Of 159 patients with a mean body mass index of 26.0 kg/m^2, the Berlin Questionnaire was positive in 16.3%, and 77 (48.4%) experienced sustained bradypnea. The median rate of cumulative sustained bradypnea time was 0.70 % (interquartile range 0.35 to 1.45) without any related factors. The incidence of immediate bradypnea and sustained and immediate hypoxemia were 58.5%, 24.5%, and 37.7%, respectively. However, none of the factors were statistically significant.

Conclusion: After cesarean delivery performed with intrathecal morphine 0.1 mg, respiratory depression events were commonly observed. However, the rate of cumulative bradypnea time was very low and there were no related factors.

Trial registration number and date of registration: UMIN Clinical Trials Registry (UMIN 0035832) and Dec. 24th, 2018

Introduction

Most women who undergo cesarean delivery experience severe postoperative pain [1, 2]. Intrathecal morphine is widely used for postoperative analgesia following cesarean delivery [3, 4]. However, there are concerns that it may cause maternal pruritus and vomiting as well as maternal respiratory depression [5, 6].

The Society for Obstetric Anesthesia and Perinatology consensus statement recommends that respiratory monitoring in low-risk pregnant women who received low-dose intrathecal morphine (0.05–0.15 mg) should be performed every 2 h for 12 h postoperatively [3]. Previous studies which monitored postpartum respiratory depression using scheduled intermittent monitoring strategy revealed low respiratory depression rates of 0%–0.26%; however, such monitoring strategy would not sufficiently detect respiratory depression and its related factors have been poorly examined [7-9]. Although some studies that used continuous monitoring, such as capnography and pulse oximeter, revealed that the incidence of

apnea and hypoxemia were much higher than those reported previously using scheduled intermittent monitoring [7, 10, 11], little evidence is available regarding bradypnea measured using continuous monitoring following intrathecal morphine in women who underwent cesarean delivery.

The aim of this study was to assess the rate of cumulative bradypnea time (total bradypnea time/total monitoring time) and its related factors in women who underwent cesarean delivery under spinal anesthesia with 0.1 mg morphine. Additionally, we aimed to evaluate the 1) time to first bradypnea event, 2) incidence of bradypnea and its related factors, 3) incidence of hypoxemia and its related factors, and 4) occurrence of clinically relevant episodes of respiratory depression.

Methods

Design and Setting

This prospective observational study was approved by the Institutional Review Board of Nara Medical University (Kashihara, Nara, Japan; Approval No. 2127) and registered with the UMIN Clinical Trials Registry (UMIN 0035832). Written informed consent was obtained from all patients. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Women aged ≥ 20 years who underwent cesarean delivery between 0700 and 2000 hours under spinal anesthesia between April 2019 and March 2020 were screened, including both elective and non-elective cases, irrespective of the gestational age. The exclusion criteria were as follows: patients with psychiatric or neuromuscular diseases; those who did not provide written informed consent; those who received anesthesia other than single-shot spinal anesthesia (multiple administrations of spinal anesthesia, epidural anesthesia, combined spinal-epidural anesthesia, and general anesthesia), those who underwent cesarean delivery following epidural labor. Women who required additional sedatives and analgesics intraoperatively, those who received oxygen administration postoperatively, those with missing data regarding demographics and respiratory monitoring, and those with respiratory monitoring within 6 hours postoperatively were excluded from data analysis[10].

In our institution, spinal anesthesia was administered with 2–2.5 ml of hyperbaric bupivacaine (0.5%), 10 μg of fentanyl, and 100 μg of morphine with the patient in the lateral position after attaching the standard anesthesia monitors. Intraoperative patient management—including blood pressure management and additional sedation and analgesia—was at the discretion of the anesthesiologist. After cesarean delivery, patients were discharged from the operating room with an adhesive acoustic respiration sensor (RAS-125™ or RAS-125™ rev C, Masimo) and an oximetry sensor (LNCS Adtx, Masimo) placed on the neck and finger, respectively, which were connected to an Acoustic Respiration Rate (RRa) pulse oximeter to monitor and regularly record RR and oxygen saturation (SpO_2). Patients were continuously monitored with the RRa device until initiation of ambulation. The RRa and SpO_2 were calculated as 10-s moving average every 2 s and 8-s moving average every 1 s, respectively, and stored in the internal memory. The

pulse oximetry data were temporarily and automatically stored in the internal memory with a 2-s resolution. After the monitoring device was detached, one of the researchers transferred the data to a storage device using TrendCom v3460 (Masimo) and saved the file. The nurses observed the patients' vital signs including their respiratory rate, postoperative pain, opioid-related adverse events (postoperative nausea, vomiting, and pruritus) every 30 minutes for up to 2 hours postoperatively and every hour for 2–24 hours postoperatively according to our institutional protocol. For postoperative pain reduction, intravenous acetaminophen (1 g) was administered four times every 6 hours; upon request for additional analgesia, pentazocine and/or flurbiprofen was administered at the discretion of the obstetrician.

Collected data

Maternal demographic data, including the age, current body mass index, gestational age, presence of hypertension including hypertensive disorder of pregnancy, and presence of diabetes mellitus were collected. The Berlin questionnaire was used to screen for obstructive sleep apnea syndrome preoperatively; it consists of the following three categories: snoring (category 1), sleepiness and fatigue on awakening (category 2), and obesity (body mass index > 30 kg/m^2) and hypertension (category 3). Each question is scored on a scale of 0–2. The scores are summed for each category; ≥ 2 points in categories 1 and 2 and ≥ 1 point in category 3 were considered positive, and ≥ 2 positive categories were representative of high risk of sleep-disordered breathing [12]. Additionally, elective or emergency surgery and administration of magnesium and ritodrine were retrieved from the electronic medical records.

Outcomes

The primary outcome of interest was the median rate of cumulative sustained bradypnea time (total sustained bradypnea time/total monitoring time) and its related factors. The secondary outcomes included the following: (1) median time to first sustained bradypnea after intrathecal morphine administration; (2) incidence of sustained and immediate bradypnea and its related factors; (3) incidence of sustained and immediate hypoxemia and related factors; and (4) occurrence of clinically relevant episode of respiratory depression, which was defined as that which required naloxone or calling the rapid response team. The following definitions were used in this study with reference previous study [13]: sustained bradypnea: respiratory rate < 8 bpm lasting at least 25 s; immediate bradypnea: respiratory rate < 8 bpm lasting at least 15 s; sustained hypoxemia: SpO_2 < 92% lasting at least 25 s; and immediate hypoxemia: SpO_2 < 92% lasting at least 15 s.

Statistical analysis

Continuous variables are presented as mean (standard deviation) and categorical variables as numbers (present). Although body mass index is a continuous variable, it was presented as a categorical variable based on the cutoff in the Berlin questionnaire asks of 30 kg/m^2. To compare the patient demographic data, univariate analysis was performed using Fisher's exact test or Mann–Whitney U test, as appropriate. Multiple regression analysis was used to assess the variables related to the cumulative sustained bradypnea time rate, in which all explanatory factors, except for body mass index and hypertension

status, were included in the Berlin Questionnaire. For evaluation of the secondary outcomes, each incidence was expressed as a percentage and each related factor was explored using multiple logistic regression analysis in which the calibration of the model was tested using the Hosmer–Lemeshow test and the area under the receiver operating characteristic curve was computed as a descriptive tool for measuring the model bias. All data were analyzed using SPSS v22.0 (IBM Inc., Armonk, NY, USA) and $P<0.05$ was considered statistically significant.

Considering the seven covariates included in the multiple regression analysis, the minimum required sample size, which was calculated using G*power v3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) with the requirements of type I (α) error, power (1-β), and effect size (f2) of 0.05, 0.95, and 0.15 (medium effect size), respectively, was found to be 153 patients. After accounting for a potential dropout rate of 30%, we decided to enroll 219 patients who met the inclusion criteria.

Results

A total of 253 women were screened; of them 219 were included in this study. However, patients who received oxygen postoperatively (n=14), patients with missing Berlin questionnaire data (n=16), and patients who lacked the data regarding postoperative respiratory monitoring (n=20) (Figure 1) were excluded. Finally, 159 patients were included in the analysis. The patient demographics are presented in Table 1. The mean body mass index was 26.0 kg/m^2, and it was ≥ 30 kg/m^2 in 20 women. Of the 159 patients, 17 (10.6%) had hypertensive disorder of pregnancy and 26 (16.3%) had a positive result on the Berlin questionnaire.

Table 1 Patient demographic data

	Total
Age (y)	33.4 (5.1)
Body mass index (kg/m^2)	
<18.5	1
18.5≤, <25	71
25≤, <30	62
30≤	25
Gestational duration (days)	261 (23)
Hypertensive disorder of pregnancy	17
Gestational diabetes	11
Emergency surgery	61
Ritodrine administration	12
Magnesium infusion	13
Positive Berlin questionnaire	26

Overall, 77 (48.4%) patients experienced sustained bradypnea. The median time interval between spinal anesthesia and the first episode of sustained bradypnea was 9.6 h (interquartile range, IQR, 3.2–17.1) and the median rate of cumulative sustained bradypnea time was 0.70% (IQR, 0.35–1.45). Table 2 presents the results of the multiple regression analysis, which indicated no statistically significant factor related to the rate of cumulative sustained bradypnea time. The incidence of immediate bradypnea and sustained and immediate hypoxemia was 58.5%, 24.5%, and 37.7%, respectively, and multiple logistic regression analysis did not reveal any statistically significant factor (Supplemental Tables 1–4). Clinically relevant episodes of respiratory depression were not observed.

Table 2 Results of multivariable regression analysis for the rate of cumulative sustained bradyapnea time

	Regression coefficient (β)	Standard error	95% Confidence Interval (lower limit, upper limit)	P-value
Age (y)	0.009	0.063	-0.11, 0.13	0.88
Gestational duration (days)	0.012	0.015	-0.01, 0.04	0.43
Gestational diabetes	0.036	1.271	-2.47, 2.54	0.97
Emergency surgery	1.102	0.694	-0.26, 2.47	0.11
Ritodrine administration	-0.159	1.413	-2.95, 2.63	0.91
Magnesium infusion	-0.773	1.469	-3.67, 2.13	0.60
Positive Berlin questionnaires	-0.448	0.875	-2.17, 1.28	0.61

Discussion

We found that almost half of the women who underwent cesarean delivery with 0.1 mg intrathecal morphine developed sustained bradypnea that was detected by the acoustic respiration sensor; however, the rate of cumulative sustained bradypnea time was as low 0.7% and without any related factors. The first episode of sustained bradypnea generally occurred several hours after spinal anesthesia. Immediate bradypnea and hypoxemia, including both sustained and immediate episodes, also commonly occurred but none of them required naloxone or a rapid response team. Furthermore, none of the factors were related to bradypnea and hypoxemia.

Capnography is the gold standard in monitoring respiratory rate; however, it requires sampling end-tidal carbon dioxide and is especially troublesome for patients without oxygen administration. Therefore, in this study, an adhesive acoustic respiration sensor was used to measure the respiratory rate. Additionally, although previous studies that used continuous monitoring reported a high incidence of respiratory depression, the total time of respiratory depression during the monitoring time was not reported. We believe that sustained and repeated respiratory depression is a more important adverse event rather than transient depression. Therefore, we primarily aimed to assess the rate of cumulative sustained bradypnea time [8, 11, 14].

In our cohort, the incidence of sustained bradypnea was as high as 48%, which is similar to the reported incidence of 53% in a previous study where end-tidal carbon dioxide < 5 mmHg for 30–120 consecutive seconds (respiratory rate < 2 bpm) was defined as apnea; similarly, the very low rate of cumulative sustained bradypnea time was comparable with the reported rate of 29 apnea events during an average of 8.5 hours of monitoring [11]. Furthermore, the incidence of hypoxemia was higher than those in some studies that used scheduled intermittent monitoring, although it was comparable with those of previous reports that performed continuous monitoring using pulse oximetry [7, 8]. However, considering that there

were no clinically relevant episodes of respiratory depression, postoperative routine continuous respiratory monitoring might be excessive in healthy women who undergo cesarean delivery with low-dose intrathecal morphine.

None of the factors were related to the rate of cumulative sustained bradypnea time. Similarly, the multiple logistic regression analyses did not identify any factors related to bradypnea and hypoxemia. In contrast, one study revealed that obstructive sleep apnea, screened using the Berlin questionnaire, was associated with desaturation events with SpO_2 < 90% for 30 seconds [8]. This could be explained by the small sample size in the multiple logistic regression analysis because, although the calibration of the model and the descriptive tool for measuring model bias were relatively valid, because our sample size was calculated for multiple regression analysis. Additionally, the small number of women with body mass index ≥ 30 kg/m^2 and positive Berlin questionnaire might have contributed to these results; therefore, further studies that can include women at high risk of respiratory depression are needed. Interestingly, previous studies have reported that women without any risks developed the highest number of apnea events, which were defined as episodes of end-tidal carbon dioxide < 5 mmHg for 30–120 consecutive seconds [11]. Although the exact reason remains unknown, this can be attributed to factors that have not been evaluated yet, such as opioid sensitivity.

Our study has several limitations. First, this was a single-center study in Japan; therefore, the generalizability of our findings may be limited. Second, our cohort included a small number of women with risk factors of respiratory depression following cesarean delivery, such as obesity and hypertension. Therefore, our results should be interpreted with caution as they are from a limited population with low risk factors. Fourth, our sample size was too small to estimate clinically relevant episodes of respiratory depression; therefore, further studies in a larger number of women are required.

In conclusion, we conducted this prospective observational study to assess postoperative bradypnea and hypoxemia in women who underwent cesarean delivery with 0.1 mg intrathecal morphine. Approximately half of the women developed episodes of sustained bradypnea; however, these episodes constituted only a small portion of the total respiratory monitoring time with no related factors. The incidences of bradypnea and hypoxemia were as high as those reported previously using continuous monitoring; however, no related factors were identified. Continuous respiratory monitoring in relatively healthy women who undergo cesarean delivery with 0.1 mg intrathecal morphine requires careful patient selection.

Declarations

Funding: None

Conflicts of Interest: None

Availability of data and material: Please contact the corresponding author

Code availability: All data were analyzed using SPSS v22.0 (IBM Inc., Armonk, NY, USA)

Author's contribution:

Hiroki Onodera: This author helped with data collection and manuscript preparation.

Mitsuru Ida: This author helped with the study design, study recruitment, data analysis, and manuscript preparation.

Yusuke Naito: This author helped with study recruitment, data analysis, and manuscript preparation.

Yuka Akasaki: This author helped with study recruitment, data collection, and manuscript preparation.

Akane Kinomoto: This author helped with study recruitment, data collection, and manuscript preparation.

Masahiko Kawaguchi: This author helped with the study design and manuscript preparation.

Ethics approval: This prospective observational study was approved by the Institutional Review Board of Nara Medical University (Kashihara, Nara, Japan; Approval No. 2127) and registered with the UMIN Clinical Trials Registry (UMIN 0035832).

Consent to participate: Written informed consent was obtained from all patients

Consent for publication: Written informed consent was obtained from all patients

Clinical Trials number and registry URL: UMIN 0035832, https://upload.umin.ac.jp/cgi-bin/ctr/ctr_menu_form_reg.cgi?recptno=R000040284

Acknowledgements: None

Author's contribution:

Hiroki Onodera: This author helped with data collection and manuscript preparation.

Mitsuru Ida: This author helped with the study design, study recruitment, data analysis, and manuscript preparation.

Yusuke Naito: This author helped with study recruitment, data analysis, and manuscript preparation.

Yuka Akasaki: This author helped with study recruitment, data collection, and manuscript preparation.

Akane Kinomoto: This author helped with study recruitment, data collection, and manuscript preparation.

Masahiko Kawaguchi: This author helped with the study design and manuscript preparation.

References

1. Kaufner L, Heimann S, Zander D, Weizsäcker K, Correns I, Sander M, Spies C, Schuster M, Feldheiser A, Henkelmann A, Wernecke KD, VON Heymann C (2016) Neuraxial anesthesia for pain control after cesarean section: a prospective randomized trial comparing three different neuraxial techniques in clinical practice. Minerva Anestesiol 82:514–524
2. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W (2013) Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 118:934–944
3. Bauchat JR, Weiniger CF, Sultan P, Habib AS, Ando K, Kowalczyk JJ, Kato R, George RB, Palmer CM, Carvalho B (2019) Society for Obstetric Anesthesia and Perinatology consensus statement: monitoring recommendations for prevention and detection of respiratory depression associated with administration of neuraxial morphine for cesarean delivery analgesia. Anesth Analg 129:458–474
4. Petersson JGR (2016) Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for obstetric anesthesia and perinatology. Anesthesiology 12:270–300
5. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B (2016) The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: a meta-analysis. Anesth Analg 123:154–164
6. Lee LA, Caplan RA, Stephens LS, Posner KL, Terman GW, Voepel-Lewis T, Domino KB (2015) Postoperative opioid-induced respiratory depression: a closed claims analysis. Anesthesiology 122:659–665
7. Abouleish E, Rawal N, Rashad MN (1991) The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 16:137–140
8. Kato R, Shimamoto H, Terui K, Yokota K, Miyao H (2008) Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. J Anesth 22:112–116
9. Crowgey TR, Dominguez JE, Peterson-Layne C, Allen TK, Muir HA, Habib AS (2013) A retrospective assessment of the incidence of respiratory depression after neuraxial morphine administration for postcesarean delivery analgesia. Anesth Analg 117:1368–1370
10. Ladha KS, Kato R, Tsen LC, Bateman BT, Okutomi T (2017) A prospective study of post-cesarean delivery hypoxia after spinal anesthesia with intrathecal morphine 150μg. Int J Obstet Anesth 32:48–53
11. Weiniger CF, Akdagli S, Turvall E, Deutsch L, Carvalho B (2019) Prospective observational investigation of capnography and pulse oximetry monitoring after cesarean delivery with intrathecal morphine. Anesth Analg 128:513–522
12. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP (1999) Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 131:485–491
13. Weiniger CF, Carvalho B, Stocki D, Einav S (2017) Analysis of physiological respiratory variable alarm alerts among laboring women receiving remifentanil. Anesth Analg 124:1211–1218

14. Terada S, Irikoma S, Yamashita A, Murakoshi T (2019) Incidence of respiratory depression after epidural administration of morphine for cesarean delivery: findings using a continuous respiratory rate monitoring system. Int J Obstet Anesth 38:32–36

Figures

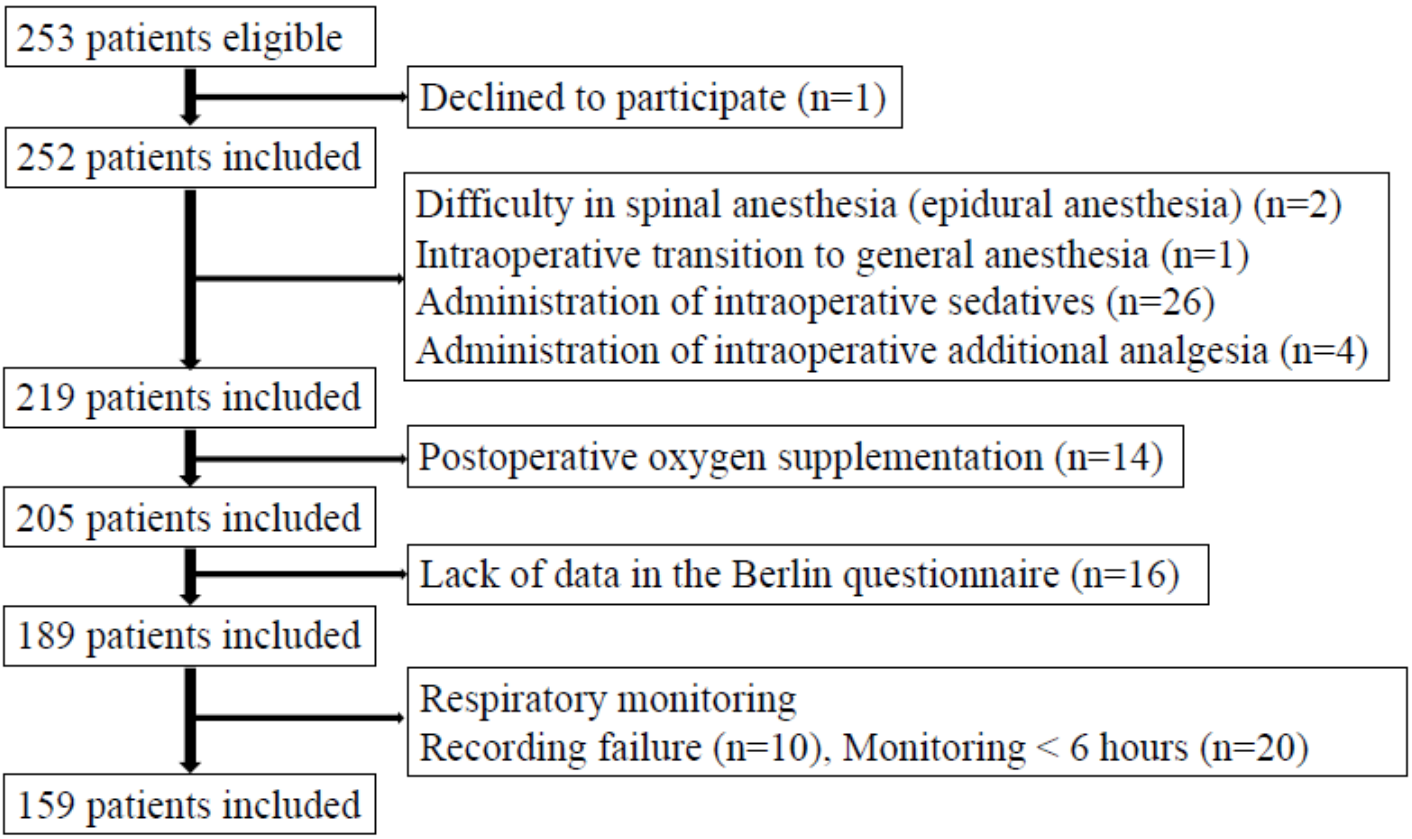

Figure 1

Patient flowchart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tablesustainbradypnea.docx