Evaluation of Different Near-Infrared Spectroscopy Devices for Assessing Tissue Oxygenation with a Vascular Occlusion Test in Healthy Volunteers

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Keywords

Healthy volunteers · Microcirculation · Oximetry

Abstract

Near-infrared spectroscopy devices can measure peripheral tissue oxygen saturation (StO₂). This study aims to compare StO₂ using INVOS[®] and different O3[™] settings (O3^{25:75} and O3^{30:70}). Twenty adults were recruited. INVOS[®] and O3[™] probes were placed simultaneously on 1 side of forearm. After baseline measurement, the vascular occlusion test was initiated. The baseline value, rate of deoxygenation and reoxygenation, minimum and peak StO₂, and time from cuff release to peak value were measured. The parameters were compared using ANOVA and Kruskal-Wallis tests. Bonferroni's correction and Mann-Whitney pairwise comparison were used for post hoc analysis. The agreement between StO₂ of devices was evaluated using Bland-Altman plots. INVOS[®] baseline value was higher (79.7 ± 6.4%) than that of O3^{25:75} and O3^{30:70} (62.4 ± 6.0% and 63.7 ± 5.5%, respectively, $p < 0.001$). The deoxygenation rate was higher with INVOS[®] (10.6 ± 2.1%/min) than with O3^{25:75} and O3^{30:70} (8.4 ± 2.2%/min, $p = 0.006$ and 7.5 ± 2.1%/min, $p < 0.001$). The min-

imum and peak StO₂ were higher with INVOS[®]. No significant difference in the reoxygenation rate was found between the devices and settings. The time to reach peak after cuff deflation was faster with INVOS[®] (both $p < 0.001$). Other parameters were similar. There were no differences between the different O3[™] settings. There were differences in StO₂ measurements between the devices, and these devices should not be interchanged. Differences were not observed between O3[™] device settings.

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Introduction

Initially, near-infrared spectroscopy (NIRS) was used to measure regional brain oxygen saturation; recently, NIRS has also been used to monitor peripheral tissue oxygen saturation (StO₂) and microvascular reactivity using the vascular occlusion test (VOT) [1, 2]. Many studies on StO₂ changes during the VOT also deal with other concepts such as association with flow-mediated dilatation [3], strategies to protect from prolonged forearm ischemia [4], and differences in vascular function between the

trained and untrained limbs [5]. StO₂ changes during the VOT can be used for microcirculation monitoring in healthy patients, aged population [6], patients with obesity [7], patients with coronary artery disease or high risks of cardiovascular diseases [8, 9], patients who undergo a cardiopulmonary bypass [10], and patients with critical illnesses such as sepsis [11, 12].

INVOS[®] (Somanetics Corp., Troy, MI, USA) was developed for measuring regional brain oxygen saturation through the use of 2 light-emitting diodes [13], and INVOS[®] has also been widely used to obtain tissue oxygen saturation in areas other than the brain and peripheral microcirculatory reactivity measurements using VOT [1, 2, 14]. O3[™] (Massimo Corp., Irvine, CA, USA) is a recently developed NIRS method that uses 4 wavelengths, and only a few studies have used this device to measure cerebral oxygen saturation [15] or StO₂ [16]. For NIRS devices, oximetry values are calculated using an assumed cerebral or tissue arterial:venous ratio (A/V ratio). The ratio differs according to the device, and the assumed ratio is 25:75 for the INVOS[®] and 30:70 for the FORE-SIGHT[®], EQUANOX[®], and NIRO[®] [17]. A previous study showed that blood pressure could affect cerebral oximetry values according to the A/V ratio [18]. O3[™] can change its preset A/V ratio between 25:75 and 30:70; therefore, it would be a useful device with an adjustable setting based on the clinical situation or blood pressure. However, no studies have compared oximetry values between these 2 different settings in VOT. In this study, we investigated the INVOS[®] and 2 different O3[™] settings (A/V ratio: 30:70 and 25:75) during VOT, and whether 2 devices were interchangeable or not in the operating room.

Participants and Methods

This study was approved by the university's institutional review board (IRB #1712-504-905), and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03395834, principal investigator: H.-S.K., date of registration: January 10, 2018). Twenty healthy volunteers aged ≥18 years, with no vascular disease, were enrolled between January and December 2018. Patients with obesity (BMI >30 kg/m²), skin pigmentation at the measurement site, pregnancy, or chronic anemia, and those taking vasoactive drugs were excluded.

NIRS Preparation

To measure tissue oxygen saturation, both the INVOS[®] 5100C Oximeter and 2 O3[™] systems were used. The INVOS[®] 5100C system utilizes near-infrared light at wavelengths that are absorbed by hemoglobin (730 and 810 nm) and the modified Beer-Lambert law technology to assess StO₂. INVOS[®] accounts for the superficial

Table 1. Demographic and hemodynamic data of volunteers

Age, years	29.3±8.5
Sex (male/female)	17/3
Height, cm	175.0±7.6
Weight, kg	69.7±9.3
Heart rate, bpm	70.4±6.4
Systolic blood pressure, mm Hg	115.8±9.6
Diastolic blood pressure, mm Hg	64.0±6.9
Mean blood pressure, mm Hg	81.2±7.3

Values are presented as mean ± SD. Hemodynamic variables were measured at baseline.

tissue using differentially spaced light detectors that incorporate the principle of spatial resolution. The distance between the probe and the 2 detectors (near and far) are 3 and 4 cm, respectively. In contrast, O3[™] systems apply the 4 different near-infrared light of wavelengths (730, 760, 805, 880 nm) and use the modified Beer-Lambert law technology. The distance between the emitter and the shallow and deep detectors were 3 and 4 cm, respectively.

The preset A/V ratios of the 2 O3[™] devices were 25:75 and 30:70, respectively. Three disposable NIRS sensors (1 INVOS[®] 5100C oximeter and 2 different O3[™] oximeter settings) were carefully applied to the medial part of the 1 side of the forearm of the volunteer, after cleaning the skin, in random order [19]. The sensors were placed 4–5 cm apart to avoid interference. As the probe position could have affected the StO₂ value of the device, we performed a total of 3 VOT measurements over 30-min intervals [20] and changed the probe position, so that each probe could be equivalently attached to the measurement site. The average StO₂ value of 3 VOT measurements from each sensor was used for analysis.

Vascular Occlusion Test

Volunteers laid down on a bed in a quiet environment with a constant room temperature of 22–24°C [14]. The initial blood pressure measurement was performed using a Solar 8000 Monitor (GE Medical Systems, GE Healthcare) 3 times at 2.5-min intervals. An adult-size blood pressure cuff with a sphygmomanometer (Calibrated[®] V-LOK[®] cuff; W.A. Baum Co., Copiague, NY, USA) was then placed around the upper arm. After baseline StO₂ value stabilized (<2% variation in 30 s) [14], the cuff was inflated to 50 mm Hg above the initial systolic blood pressure and maintained for 3 min [21]. After 3 min of VOT, the cuff was rapidly deflated, within a second. Data were collected until StO₂ values returned to baseline. The INVOS[®] StO₂ values were changed every 4–5 s, and the O3[™] values were changed every 2 s according to the default setting of each device, as we could not change the settings of the devices. All the StO₂ data were automatically saved in each device during the whole procedure, and StO₂ value change was recorded for backup purposes into the personal computer and analyzed.

The following VOT variables were used for the analysis: baseline StO₂ (%), deoxygenation rate from baseline until nadir (%/min), minimum StO₂ (%), peak StO₂ (%), and ΔStO₂ (%); the difference between the baseline and minimum StO₂ values, reoxygenation rate at the first 10 s after cuff deflation (%/s), reoxygenation rate from minimum until the peak value (%/min), and elevation time (s); time from cuff release to peak value, StO₂ overshoot (%);

Table 2. Comparison between 3 devices of the different variables

	O3 ^{25:75}	O3 ^{30:70}	INVOS [®]
Baseline StO ₂ , %*	62.3±5.8	63.2±5.8	79.7±6.4
Deoxygenation rate, %/s*	0.14±0.04	0.13±0.03	0.18±0.03
Minimum StO ₂ , %*	37.6±10.6	40.9±9.2	47.6±8.9
Maximum StO ₂ , %*	80.7 (79.7–84.3)	81.5 (80.4–84.3)	95 (94.6–95.0)
ΔStO ₂ , %*	24.9±7.4	22.8±5.8	30.6±9.3
Reoxygenation rate at first 10 s after cuff deflation, %/s	2.59±1.04	2.38±0.81	2.86±0.76
Reoxygenation rate from minimum to maximum StO ₂ , %/s	155.1±62.5	142.7±48.6	171.7±45.4
Reaction time, s*	9.8±1.3	9.6±1.3	4.2±1.4
Rise time, s*	27.1±5.3	28.5±6.7	16.5±2.8
Area under the hyperemic curve (% × min)	29.9±17.1	26.4±11.0	27.9±12.4
Settling time, s	2.8±0.6	2.8±0.6	2.7±0.4

Values are presented as mean ± SD, or median (IQR). StO₂, tissue oxygen saturation. * $p < 0.05$ from ANOVA between O3^{25:75}/O3^{30:70} and INVOS. No statistical difference between O3^{25:75} and O3^{30:70} in all variables.

difference between the peak StO₂ and baseline StO₂; and settling time, time from cuff release to baseline StO₂ value (s) [19–21].

The ischemic phase was analyzed for the deoxygenation rate from baseline until nadir (%/min), minimum StO₂ after 3 min of ischemia (%), and ΔStO₂ (%; i.e., the difference between the baseline and minimum StO₂ values). The deoxygenation rate from baseline until nadir is generally considered to reflect muscle metabolism, and the minimum StO₂ is considered to indicate the extent of ischemia. The reperfusion phase was analyzed for reoxygenation rate from minimum until peak value (%/min) and elevation time (s). Although these parameters are directly related to StO₂, the reoxygenation rate from the minimum to the peak value is metabolism dependent, as it is based on the ΔStO₂ after a fixed time of occlusion, while the elevation time solely represents the time required by the oxygenated arterial blood during reperfusion to wash out the stagnantly deoxygenated blood. The hyperemic phase of the VOT was analyzed for peak StO₂ during reperfusion (%), StO₂ overshoot (i.e., difference between peak and baseline StO₂ values), the area under the hyperemic curve (% min), and the settling time from release of the cuff to recovery to the baseline StO₂ value (min). According to a previous study, a 10-s window slope analysis is a repeatable and reliable measurement of vascular response and showed a strong positive correlation with FMD [22].

Statistical Analysis

Statistical analyses were performed using the SPSS Statistics 22 software (SPSS Inc., Chicago, IL, USA) and MedCalc software (ver. 12.7.7; MedCalc Software, Ostend, Belgium). The raw data were tested for normality using the Kolmogorov-Smirnov test. Data were expressed as mean ± SD or median (interquartile range [IQR]).

Deoxygenation and reoxygenation rates were calculated as (baseline – minimum)/time of ischemia and (peak – minimum)/time of reperfusion, respectively. An ANOVA and Kruskal-Wallis test comparison were used to evaluate the difference between each device. For the post hoc analysis, Bonferroni's correction and Mann-Whitney pairwise test were used. The agreement between StO₂ during the resting period and the ischemia measured by different devices was evaluated using a modified Bland-Altman

method. A p value of <0.05 was considered to be statistically significant. This article adheres to the applicable TREND guidelines, as possible.

Results

A total of 20 healthy volunteers were enrolled and completed the study. Demographic and baseline hemodynamic data are provided in Table 1. The variables that were used for the comparisons between devices are summarized in Table 2. The INVOS[®] baseline StO₂ value (79.7 ± 6.4%) was higher than that of O3^{25:75} and O3^{30:70} (62.3 ± 5.8% and 63.2 ± 5.8%, respectively, both $p < 0.001$). The 95% confidence intervals of the differences between INVOS[®] and O3^{25:75} and O3^{30:70} were 12.5–22.0% and 11.3–20.7%, respectively.

The bias, which was calculated using the Bland-Altman method, between the baseline StO₂ values of INVOS[®] and of O3^{25:75}/O3^{30:70} were 17.1%/15.6%, and the limits of agreement were 5.4–28.8%/2.4–28.9%, respectively (Fig. 1). There were no statistically significant differences between the 2 A/V ratios of the O3TM devices.

During the VOT, the INVOS[®] StO₂ (10.6 ± 2.1%/min) decreased more rapidly than that of O3^{25:75} and O3^{30:70} (8.4 ± 2.2%/min and 7.5 ± 2.1%/min, $p = 0.006$ and $p < 0.001$, respectively). During cuff inflation, the bias between the StO₂ values of INVOS[®] and of O3^{25:75}/O3^{30:70} was 2.1/3.0%, and the limits of agreement were –0.1 to 4.3%/0.5–5.4%, respectively. The Pearson correlation coefficient between StO₂ changes during cuff inflation of INVOS[®] and O3^{25:75}/O3^{30:70} was 0.784/0.860 ($p < 0.01$).

Fig. 1. Bland-Altman analysis of mean bias and baseline agreement limits among 3 devices INVOS[®] versus O3^{30:70} (a) INVOS[®] versus O3^{25:75} (b) O3^{30:70} versus O3^{25:75} ($n = 20$) (c). Solid line, mean bias; dashed line, agreement limits.

The Pearson correlation coefficient between O3^{25:75}/O3^{30:70} was 0.829 ($p < 0.01$). In addition, ΔStO_2 was relatively lower in O3^{25:75}/O3^{30:70} than in INVOS[®], with a statistical significance ($p < 0.05$).

At the end of VOT, the minimal StO_2 of INVOS[®] ($47.6 \pm 8.9\%$) was significantly higher than that of O3^{25:75} ($37.6 \pm 10.6\%$, $p = 0.006$) but did not significantly differ from O3^{30:70} ($40.9 \pm 9.2\%$, $p = 0.106$). After cuff release, the StO_2 values of the 3 devices increased rapidly and reached peak values. The StO_2 overshoot was similar in the 3 comparisons. However, there was a gap between cuff release and the time at which StO_2 values started to change. The time from cuff release to peak value was also shorter in INVOS[®] (16.5 ± 2.8 s) than in O3^{25:75}/O3^{30:70} ($27.1 \pm 5.3/28.5 \pm 6.7$ s, both $p < 0.001$). The peak StO_2 value of INVOS[®] was 95% (94.6–95.0), which was significantly higher than that of O3^{25:75}/O3^{30:70} (80.7% [79.7–84.3]/81.5% [80.4–84.3], both $p < 0.001$). However, the peak StO_2 value of INVOS[®] in most cases was 95%, which is the upper limit of the measurable range of INVOS[®]. In contrast, the peak StO_2 value of O3^{25:75}/O3^{30:70} was variable and did not reach the upper measurement range limit in all cases, which was 95%, according to a previous study [16]. Furthermore, the INVOS[®] reoxygenation rate ($171.7 \pm 45.4\%/min$) did not significantly differ from O3^{25:75}/O3^{30:70} ($155.1 \pm 62.5/142.7 \pm 48.6\%/min$, $p = 0.273$). The reoxygenation slope in 10 s was calculated and is shown in Table 2. No significant difference was found between the devices and their settings. During the hyperemic phase, the area under the hyperemic curve was similar between the devices and settings of the Massimo device. In addition, the setting time was not different in all the comparisons. No significant complications occurred during the study.

Discussion

In this study, we evaluated StO_2 measurements by INVOS[®] and 2 different O3TM settings (A/V ratios: 30:70 and 25:75) in 3-min VOTs in healthy volunteers. The baseline StO_2 and variables that were obtained during VOT significantly differed between the 2 devices. However, no significant difference was found between the 2 O3TM A/V ratios. In addition, several meaningful parameters related to a VOT were similar in spite of the absolute values of StO_2 or t .

O3TM is a recently developed NIRS, and only 2 clinical trials have used this device until now. In a study, this de-

vice could appropriately predict cerebral regional oxygen saturation [15]. The other study reported that peripheral tissue oxygenation was measured during ischemic preconditioning during cardiac surgery, and the results showed a correlation between O3TM and another NIRS (EQUANOX[®]) device, which has been used to monitor peripheral tissue oxygenation [16]. However, in this study, the study group included patients with cardiac disease, and the deoxygenation and reoxygenation rates during VOT were not measured, which reflects tissue oxygen extraction and microvascular reactivity.

The assumed A/V ratio of NIRS is not uniform. The A/V ratio of INVOS[®] is 25:75, and the A/V ratio of O3TM can be changed between 25:75 and 30:70. The NIRS A/V ratio was initially based on cerebral arterial and venous blood volumes. However, the actual cerebral A/V ratio is not a fixed value. In addition to interindividual arterial and venous blood volume differences, the cerebral A/V ratio dynamically changes with hypoxia and arterial carbon dioxide tension change [17, 23]. In the peripheral tissue, these dynamic changes would not occur, and blood flow is limited during the VOT [24]. Until now, no study has investigated the appropriate A/V ratio for peripheral tissue analyses. This is because there is no reference method for peripheral tissue oxygen saturation and desaturation and reperfusion slopes during VOT, and values other than StO₂ have been hypothesized to provide information about tissue oxygen metabolism and microvascular reactivity in previous studies [1, 10, 11]. However, the determination of whether different NIRS devices are interchangeable for StO₂ measurements is clinically important, and many studies have investigated this issue [14, 16]. Thus, we aimed to investigate whether NIRS StO₂ values are influenced by different A/V ratios. Although the average baseline, peak, and minimum StO₂ values were slightly higher in O3^{30:70}, there was no statistically significant difference in StO₂ values between the 2 O3TM settings. Furthermore, the deoxygenation rate, reoxygenation rate, and response time were almost identical in the 2 settings. In addition, while there were significant differences between the INVOS[®] and O3 devices, the minimum values were not significantly different. Our study suggests that the A/V ratio is not a major factor that contributes to the differences between NIRS devices.

In response to cuff release, the StO₂ value change was more prompt in the INVOS[®] device than in the O3TM. The time from cuff release to peak value was shorter, and the time to peak value after the StO₂ value started to change was also significantly shorter in INVOS[®] (12.3 [9.7–14.7]) than in O3^{25:75}/O3^{30:70} (16.3 [14.5–16.3]/18.3 [14.7–18.3],

respectively, both $p < 0.001$), despite that the StO₂ value changed every 4–5 s for the INVOS[®] device and every second for the O3TM. The fast INVOS[®] device response to oxygenation change has also been reported in a previous study that compared INVOS[®] with FORE-SIGHT[®] [21]. This faster rate of change could be attributed to better detection; however, cutaneous contamination or greater StO₂ value variability could also result in similar effects. Since no StO₂ reference method exists, it is impossible to determine which modality is most valid [21].

Interestingly, although the peak INVOS[®] value was higher than that of O3TM, the reoxygenation rate and reoxygenation rate at first 10 s after cuff deflation did not significantly differ. In contrast, the INVOS[®] deoxygenation rate was higher than that of O3TM. One possible explanation is that the peak INVOS[®] StO₂ value was 95% in most cases, which is the upper limit of the INVOS[®] measure range, and this result was also observed in previous studies [14]. Because of this “ceiling effect,” the amount of hyperoxygenation with INVOS[®] remains uncertain.

The differences in the measured values between the 2 NIRS instruments could be explained by several factors. First, technical and wavelength differences were observed between the 2 NIRS systems. They use a similar spatial resolution mechanism, in which StO₂ values are determined by subtracting superficial tissue interference. Also, both devices use 1 light source and 2 optodes, with distances of 3 and 4 cm, respectively. However, INVOS[®] uses 2 wavelengths (730 and 810 nm) and O3 uses 4 wavelengths, but the actual O3 wavelengths are unknown. The number of NIRS device wavelengths varies. In previous studies that compared NIRS devices that use different numbers of wavelengths, significant differences were found in both absolute values and dynamic measurements, even with similar measurement technologies [21]. Furthermore, in a study that compared 2 NIRS devices that use 4-wavelength technology, similar trends were found between EQUANOX and O3TM, while the limits of agreement were large, which suggests that both devices are not interchangeable in clinical practice [16]. In that study, the baseline values were not the same as those of our study (68 vs. 63.2%) but certainly lower than the values obtained with the INVOS[®] device. Another study reported 4-wavelength NIRS values lower than the INVOS[®] device values, which implies the relative lower baseline 4-wavelength NIRS value, although the exact reason is uncertain [25]. Theoretically, NIRS devices that use more wavelengths would be more accurate and have enhanced tissue recognition [21]. However, no published studies have examined the superiority of 4-wavelength NIRS systems over others,

and since no reference value exists for measuring peripheral tissue oxygen saturation, it is difficult to say whether 1 NIRS device is more accurate than another [16]. Second, despite the technological similarities, the optical technology and computational algorithms that are used to derive actual oxygen saturation values may differ between devices, and these values are derived from various assumptions that may not be error free [21]. Access to raw optical data and algorithms, which are kept confidential in different companies, could clarify this issue. In addition, the values of most NIRS devices could not represent a real tissue saturation value because the actual path length was not clarified, and this point might be considered for the evaluation or analysis of results from NIRS devices.

A recent study suggested a necessity to normalize the ischemic stimulus when evaluating the reperfusion phase [6]. In this study, lower minimum StO₂ values at the peripheral tissue may cause a steeper reoxygenation rate, higher peak values, or greater area under the curve during the reactive hyperemic phase, and this finding is not compatible with the result of our study. However, the difference was caused by the physiological difference between the study participants (young vs. elderly). We performed the VOT with 2 different devices simultaneously in the same participant, and the different values of the devices did not show physiological differences. Therefore, our study result could indicate that the 2 devices showed the difference response at the same physiological change. As a result, the devices might not be compatible with each other. If this study is performed in the young and elderly participants with 2 devices, we could compare the differences among the devices in the different age groups.

There are several limitations to this study. First, unlike previously reported investigations, there was a strong interference between different NIRS probes, and it was not possible to gain StO₂ values if probes were directly attached side to side. We did our best to reduce the interference between the probes by occluding the dressing that goes over the probes. We had to apply probes 4–5 cm apart from the other probe, which makes the measurement site uneven. Therefore, we had to repeat VOT measurements 3 times per case, while changing the probe arrangement in a random order. The 30-min rest time was sufficient based on previous studies [20], where no differences were found in baseline, peak StO₂, and reoxygenation rate in each VOT. Differences were present in the deoxygenation rates of the first VOT and second VOT, but the gap was small, and no differences were observed between the second VOT and following VOTs in that study. Second, male subjects were dominant in our study population. In previous studies, sex

differences may exist, depending on NIRS devices [14]. However, prior studies were usually limited to baseline StO₂ measurements, and no difference was observed between dynamic parameters. Considering that baseline StO₂ levels were higher in male subjects than in a previous study that used INVOS® [14], our study results correlate well with these findings. Third, the optimal VOT method remains controversial, especially for cuff deflation thresholds and probe measurement sites. As described earlier, the purpose of our study was to compare different NIRS systems during same VOT and minimize the bias that results from measuring the left or right side of the forearm. Therefore, we measured StO₂ of same side of the forearm and used a time-dependent deflation cutoff of 3 min. Finally, we applied a 3-min occlusion test instead of a 5-min occlusion period. A recent study reported that several different VOT durations showed different parameter values and reliability, and the 5-min occlusion period was preferred over the 3-min period [26]. However, the differences in the parameters were relatively small in the previous study, and the bias from the duration was insignificant in the present study. Although the absolute values were different, the important parameters of the VOT were similar. In addition, the 5-min occlusion test induced discomfort and pain to the participants, and hence, a 3-min occlusion test was applied.

Novelty and Conclusion

In conclusion, there were significant differences in tissue oxygen saturation measurements between O3™ and INVOS® devices, and these devices are not interchangeable. However, a significant difference was not present in the assumed A/V ratio of O3™, and further studies are required to determine whether the A/V ratio is appropriate for measuring peripheral oxygen saturation.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest Statement

The authors declare that no external funding and no competing interests for this work.

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Author Contributions

H.-K.: This author designed the study, analyzed the data, wrote the paper, and revised the paper. J.-T.K.: This author designed the study and revised the paper. J.-H.L.: This author con-

ducted the study, collected data, and revised the paper. E.-H.K.: This author conducted the study, collected data, and revised the paper. Y.-E.J.: This author conducted the study, collected data, and revised the paper. S.-H.J.: This author conducted the study, collected data, and revised the paper. J.C.: This author conducted the study, collected data, wrote the paper, and revised the paper.

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