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## Accuracy of two pulse-oximetry measurements for INTELLiVENT-ASV in mechanically ventilated patients: a prospective observational study

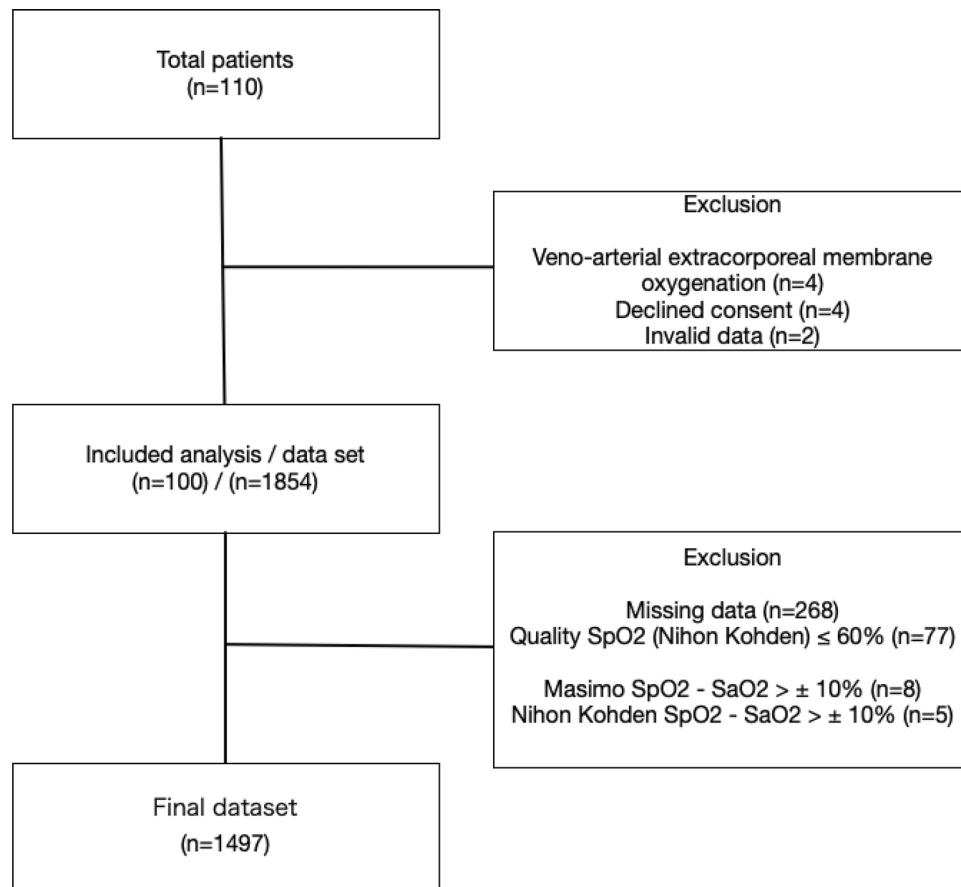
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Recently, maintaining a certain oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) range in mechanically ventilated patients was recommended; attaching the INTELLiVENT-ASV to ventilators might be beneficial. We evaluated the SpO<sub>2</sub> measurement accuracy of a Nihon Kohden and a Masimo monitor compared to actual arterial oxygen saturation (SaO<sub>2</sub>). SpO<sub>2</sub> was simultaneously measured by a Nihon Kohden and Masimo monitor in patients consecutively admitted to a general intensive care unit and mechanically ventilated. Bland–Altman plots were used to compare measured SpO<sub>2</sub> with actual SaO<sub>2</sub>. One hundred mechanically ventilated patients and 1497 arterial blood gas results were reviewed. Mean SaO<sub>2</sub> values, Nihon Kohden SpO<sub>2</sub> measurements, and Masimo SpO<sub>2</sub> measurements were 95.7%, 96.4%, and 96.9%, respectively. The Nihon Kohden SpO<sub>2</sub> measurements were less biased than Masimo measurements; their precision was not significantly different. Nihon Kohden and Masimo SpO<sub>2</sub> measurements were not significantly different in the “SaO<sub>2</sub> < 94%” group ( $P = 0.083$ ). In the “94% ≤ SaO<sub>2</sub> < 98%” and “SaO<sub>2</sub> ≥ 98%” groups, there were significant differences between the Nihon Kohden and Masimo SpO<sub>2</sub> measurements ( $P < 0.0001$ ;  $P = 0.006$ ; respectively). Therefore, when using automatically controlling oxygenation with INTELLiVENT-ASV in mechanically ventilated patients, the Nihon Kohden SpO<sub>2</sub> sensor is preferable. *Trial registration* UMIN000027671. Registered 7 June 2017.

Avoiding both hypoxemia and hyperoxemia is vital in critically ill patients<sup>1–4</sup>. Because hypoxemia poses the risk of tissue hypoxia, adequate oxygen should be prescribed for ventilation. In contrast, hyperoxemia has been associated with increased mortality<sup>5</sup> and fewer ventilator-free days<sup>6</sup>. Pulse oximetric oxygen saturation (SpO<sub>2</sub>) monitor is widely used in clinical situation to monitor hypoxemia. However, hyperoxemia is frequently under-recognized when PaO<sub>2</sub> is over 100 mmHg, because SpO<sub>2</sub> is difficult to determine the level of PaO<sub>2</sub> in this situation. In regard to the oxygen delivery, it is recommended that arterial oxygen saturation (SaO<sub>2</sub>) be kept at a certain range in mechanically ventilated patients. Recently, a multicentre randomised trial suggested that maintaining the oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) at 97% might be ideal for managing critically ill patients<sup>7</sup>. From the British Thoracic Society guidelines, the target saturation range for acutely ill patients who are not at risk of hypercapnic respiratory failure is 94–98%<sup>8</sup>. Despite the control and maintenance of adequate oxygen saturation targets, hyperoxemia has been reported in some critically ill patients<sup>9</sup>; approximately one out of three patients were managed with SpO<sub>2</sub> > 97%. One reason for unresolved hyperoxemia was the fluctuations in the oxygenation status. In mechanically ventilated patients, despite setting an adequate SpO<sub>2</sub> range, SpO<sub>2</sub> can easily change due to posture, respiratory pattern, and the presence of airway secretions. Thus, it might be difficult to strictly control the oxygenation status within the ideal SpO<sub>2</sub> range manually.

INTELLiVENT-ASV is one of the unique ventilator modes which available only for Hamilton Medical ventilators. It has the original function which allow to monitor patients' SpO<sub>2</sub> and end-tidal carbon dioxide (E<sub>T</sub>CO<sub>2</sub>) and automatically control the delivered fraction of inspired oxygen (F<sub>I</sub>O<sub>2</sub>) and minute ventilation volume<sup>10,11</sup>. The automatic F<sub>I</sub>O<sub>2</sub> control function can be used with the SpO<sub>2</sub> monitoring probe attached to the ventilator. Generally, SpO<sub>2</sub> is controlled from 93 to 97% in normal lung setting by adjusting F<sub>I</sub>O<sub>2</sub> between 0.21 and 1.0, but

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**Figure 1.** Patients' flow chart.

SpO<sub>2</sub> target range can also easily alter depend on each patients' clinical situation. Because INTELLiVENT-ASV is able to monitor and adjust oxygen breath by breath continuously, it is easier to use INTELLiVENT-ASV than a physician-driven control to maintain an appropriate SpO<sub>2</sub> range. However, it is unclear how accurate the SpO<sub>2</sub> measured during INTELLiVENT-ASV compared to the actual SaO<sub>2</sub>. Several studies have suggested that SpO<sub>2</sub> measurements tend to overestimate the oxygenation status in critically ill patients<sup>12–14</sup>. In addition, few studies have evaluated the relationship between actual SpO<sub>2</sub> and SaO<sub>2</sub> using either the Nihon Kohden or the Masimo pulse oximeter, which are the only two available for INTELLiVENT-ASV<sup>15</sup>.

In this study, we aimed to compare the accuracy of bias and precision of the two pulse oximeters in mechanically ventilated patients in an intensive care unit (ICU) setting. In addition, we evaluated the accuracy of SpO<sub>2</sub> measurements in various SaO<sub>2</sub> range categories.

## Results

**Enrolment and baseline characteristics.** In total, the results of 1854 blood gas analyses performed in 100 patients ventilated with HAMILTON G5 ventilator (Hamilton Medical AG, Rhäzüns, Switzerland) were considered for evaluation (Fig. 1). Of these results, the following were excluded: those with missing data on the Nihon Kohden and Masimo SpO<sub>2</sub> measurements (n = 268), those in which the Nihon Kohden SpO<sub>2</sub> measurements were ≤ 60% (n = 77), those in which the difference in value between the Nihon Kohden SpO<sub>2</sub> measurement and the actual SaO<sub>2</sub> was > 10% (n = 5), and those in which the difference in value between the Masimo SpO<sub>2</sub> measurement and the actual SaO<sub>2</sub> was > 10% (n = 8).

Table 1 shows the characteristics of patients ventilated with a HAMILTON G5 ventilator. The mean value of the blood gas analyses was  $15.0 \pm 15.4$ , mean Acute Physiology and Chronic Health Evaluation II score was  $24.6 \pm 8.3$ , and the mean duration of mechanical ventilation was  $9.0 \pm 7.4$  days. The arterial oxygen tension (PaO<sub>2</sub>)/F<sub>I</sub>O<sub>2</sub> ratio was 249.6, categorised into PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> > 300 (26%),  $200 < \text{PaO}_2/\text{F}_I\text{O}_2 \leq 300$  (36%),  $100 < \text{PaO}_2/\text{F}_I\text{O}_2 \leq 200$  (22%), and PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ≤ 100 (16%). ICU and hospital mortality rates were 5.0% and 16.0%, respectively.

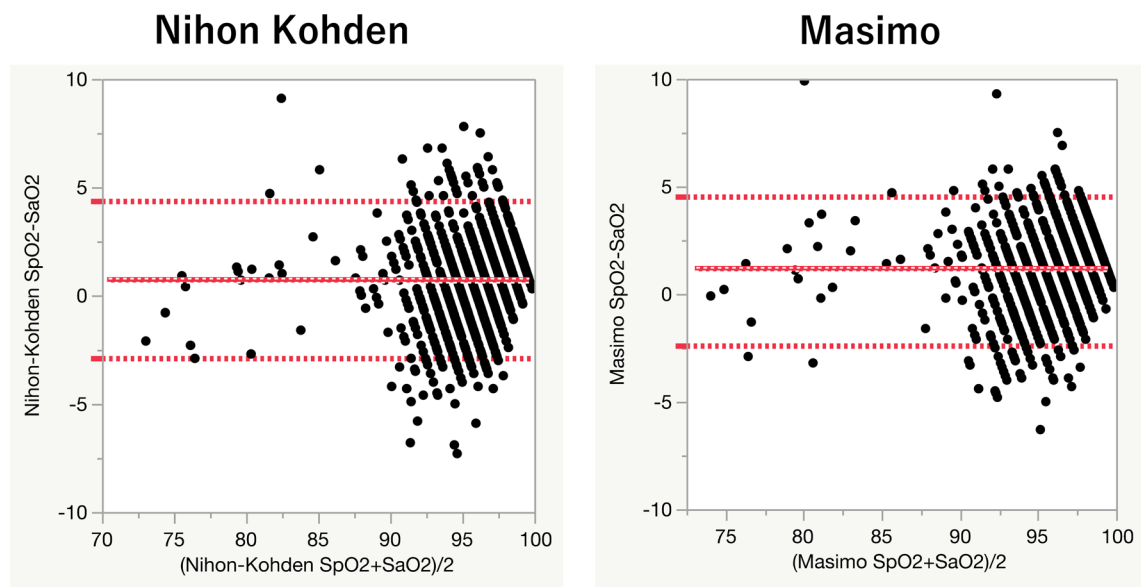
**Bland–Altman plot comparing SpO<sub>2</sub> and SaO<sub>2</sub>.** A Bland–Altman plot was generated to evaluate bias and precision (Fig. 2). Mean SpO<sub>2</sub> was 96.4% using the Nihon Kohden and 96.9% using the Masimo monitor. The bias was lower in the Nihon Kohden SpO<sub>2</sub> measurements than in the Masimo measurements, although the precision was not significantly different (mean ± SD,  $0.72 \pm 1.86\%$  vs  $1.17 \pm 1.68\%$ , respectively: Table 2).

Mean $\pm$ SD	n = 100
Age (years)	63.3 $\pm$ 15.3
Height (cm)	158.7 $\pm$ 9.3
Weight (kg)	60.1 $\pm$ 15.9
Body mass index	23.7 $\pm$ 5.1
Male	48 (48%)
Number of Blood gas analysis (25th–75th percentile)	15.0 $\pm$ 15.4
Acute Physiology and Chronic Health Evaluation II	24.6 $\pm$ 8.3
<b>Classification of disease</b>	
Respiratory	36 (36%)
Cardiovascular	9 (9%)
Gastrointestinal	35 (35%)
Neurological	9 (9%)
Haematological	2 (2%)
Trauma	3 (3%)
Gynaecology	2 (2%)
Other	4 (4%)
<b>Co-morbidity</b>	
Hypertension	43 (43%)
Ischaemic heart disease	8 (8%)
Chronic heart failure	6 (6%)
Arrhythmia	8 (8%)
COPD	7 (7%)
Cerebrovascular accident	6 (6%)
Diabetes mellitus	20 (20%)
Chronic kidney disease on haemodialysis	5 (5%)
hepatic disease	11 (11%)
<b>Blood gas analysis (including all analyses, n = 1497)</b>	
pH	7.426 $\pm$ 0.081
PaO <sub>2</sub> , mmHg	92.5 $\pm$ 35.1
PaCO <sub>2</sub> , mmHg	40.4 $\pm$ 8.9
Haemoglobin, g/dL	9.3 $\pm$ 1.8
SaO <sub>2</sub> , %	95.7 $\pm$ 2.9
MV duration, days	9.0 $\pm$ 7.4
PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> (day 1)	249.6 $\pm$ 143.6
PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> > 300	26 (26%)
200 < PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> $\leq$ 300	36 (36%)
100 < PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> $\leq$ 200	22 (22%)
PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> $\leq$ 100	16 (16%)
Veno-venous extracorporeal membrane oxygenation	2 (2%)
ICU days	10.3 $\pm$ 7.6
ICU mortality	5 (5%)
Hospital mortality	16 (16%)

**Table 1.** Patient characteristics. COPD chronic obstructive pulmonary disease, ICU intensive care unit, SaO<sub>2</sub> arterial oxygen saturation, SpO<sub>2</sub> pulse-oximetric oxygen saturation, PaCO<sub>2</sub> arterial carbon dioxide tension, PaO<sub>2</sub> arterial oxygen tension.

We also analysed all raw data, including outliers. The bias improved slightly in the Masimo; however, the precision deteriorated in the Masimo measurements compared to the Nihon Kohden measurements (0.72  $\pm$  2.07% vs 1.08  $\pm$  2.42%) (see Supplementary Table S1 and Supplementary Fig. S1).

**Differences between SaO<sub>2</sub> and pulse oximeters' SpO<sub>2</sub> among SaO<sub>2</sub> categories.** Among the three SaO<sub>2</sub> range categories (SaO<sub>2</sub> < 94%, 94%  $\leq$  SaO<sub>2</sub> < 98%, and SaO<sub>2</sub>  $\geq$  98%), we evaluated the differences in SpO<sub>2</sub> measurements by both monitors within each group (Fig. 3 and Table 3). In the “SaO<sub>2</sub> < 94%” group, there was no significant difference between the Nihon Kohden SpO<sub>2</sub> measurements and the Masimo measurements (1.41  $\pm$  2.28% vs 1.74  $\pm$  2.15%,  $P = 0.083$ ). However, in the “94%  $\leq$  SaO<sub>2</sub> < 98%” and “SaO<sub>2</sub>  $\geq$  98%” groups, there were significant differences between the Nihon Kohden SpO<sub>2</sub> measurements and the Masimo measurements (0.57  $\pm$  1.77% vs 1.10  $\pm$  1.60%,  $P < 0.0001$ ; 0.51  $\pm$  1.49% vs 0.84  $\pm$  1.28%,  $P = 0.006$ ; respectively), although there



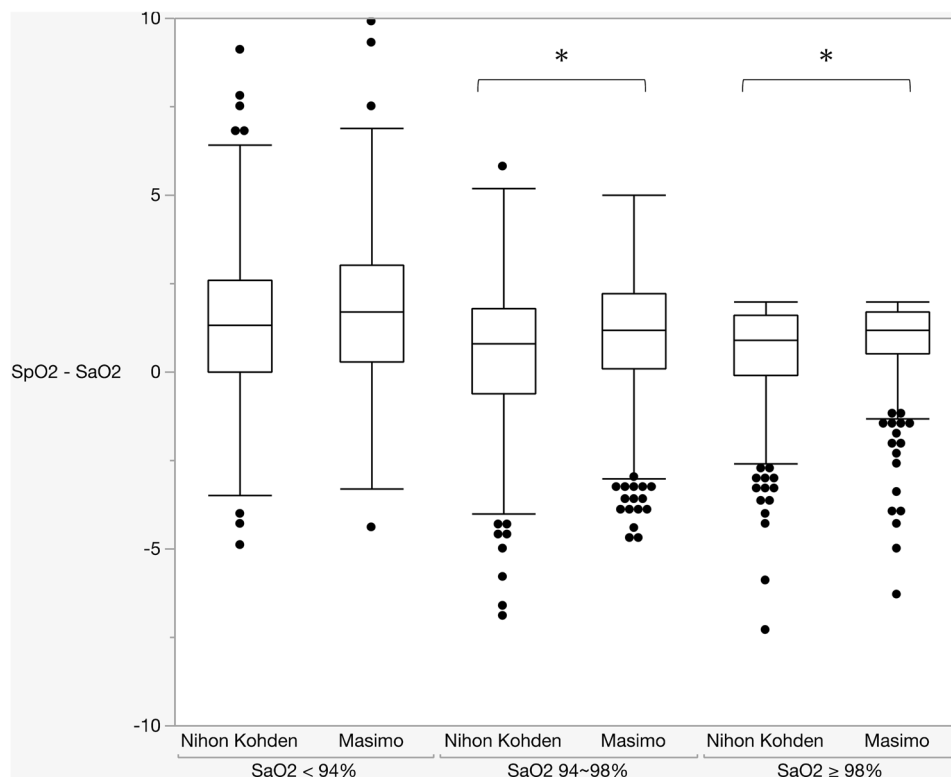
**Figure 2.** Bland–Altman plot comparing SaO<sub>2</sub> and SpO<sub>2</sub>. The horizontal axis represents (SpO<sub>2</sub> + SaO<sub>2</sub>)/2. The vertical axis represents SpO<sub>2</sub> – SaO<sub>2</sub>. The middle horizontal red line represents bias. The upper horizontal red dotted line represents the upper limits of agreement, and the lower horizontal red dotted line represents the lower limits of agreement. Black dots represent each test result. The left figure portrays Nihon Kohden SpO<sub>2</sub>, and the right figure portrays Masimo SpO<sub>2</sub>.

	Mean (95% CI)
<b>Blood gas analysis</b>	
SaO <sub>2</sub>	95.72% (95.57–95.86)
<b>Nihon Kohden SpO<sub>2</sub></b>	
SpO <sub>2</sub>	96.4% (96.3–96.6)
Bias (SpO <sub>2</sub> –SaO <sub>2</sub> )	0.72% (0.62–0.81)
Precision	1.86 (1.78–1.95)
Upper limits of agreement	4.37 (4.11–4.63)
Lower limits of agreement	–2.93 (–3.20 to –2.69)
<b>Masimo SpO<sub>2</sub></b>	
SpO <sub>2</sub>	96.9% (96.7–97.1)
Bias (SpO <sub>2</sub> –SaO <sub>2</sub> )	1.17% (1.08–1.26)
Precision	1.68 (1.61–1.77)
Upper limits of agreement	4.46 (4.24–4.73)
Lower limits of agreement	–2.12 (–1.90 to –2.39)

**Table 2.** Bias and precision for each pulse oximeter (n = 10 000). CI confidential interval, SaO<sub>2</sub> arterial oxygen saturation, SpO<sub>2</sub> pulse-oximetric oxygen saturation.

was a slight difference of -3% or more compared to actual SaO<sub>2</sub> and the difference was larger than Masimo SpO<sub>2</sub> in “SaO<sub>2</sub> ≥ 98%” group (Table 3).

**Area under the receiver operating characteristic curve to detect SaO<sub>2</sub> < 90% and SaO<sub>2</sub> ≥ 98%.** We evaluated each pulse oximeter’s ability to detect SaO<sub>2</sub> < 90%. The area under the receiver operating characteristic curves (AUCs) were 0.966 using the Nihon Kohden and 0.971 using the Masimo monitor. When cut off point was set at SpO<sub>2</sub> 90% in Nihon Kohden and Masimo, its sensitivity and specificity were 62.8% and 99.0% in Nihon Kohden SpO<sub>2</sub>, and 56.9% and 99.3% in Masimo SpO<sub>2</sub>, respectively. There was no statistically significant difference in the AUCs between both monitors ( $P = 0.530$ ). Regarding SaO<sub>2</sub> ≥ 98%, the AUCs were 0.837 using the Nihon Kohden and 0.835 using the Masimo monitor. When cut off point was set at SpO<sub>2</sub> 98% in Nihon Kohden and Masimo, its sensitivity and specificity were 87.1% and 66.2% in Nihon Kohden SpO<sub>2</sub>, and 90.8% and 58.7% in Masimo SpO<sub>2</sub>, respectively. However, there was no statistically significant difference in the AUCs of both monitors ( $P = 0.841$ ; Fig. 4).



**Figure 3.** Differences in the pulse oximeters'  $SpO_2$  measurements among  $SaO_2$  categories. Three  $SaO_2$  categories were established ( $SaO_2 < 94\%$ ,  $94\% \leq SaO_2 < 98\%$ ,  $SaO_2 \geq 98\%$ ). The vertical axis represents  $SpO_2 - SaO_2$ , the horizontal axis represents Nihon Kohden  $SpO_2$  and Masimo  $SpO_2$  for each of the three groups. There were significant differences in the groups with  $SaO_2 \geq 94\%$ . However, there was no significant difference in the  $SaO_2 < 94\%$  group. \*:  $P < 0.005$ .

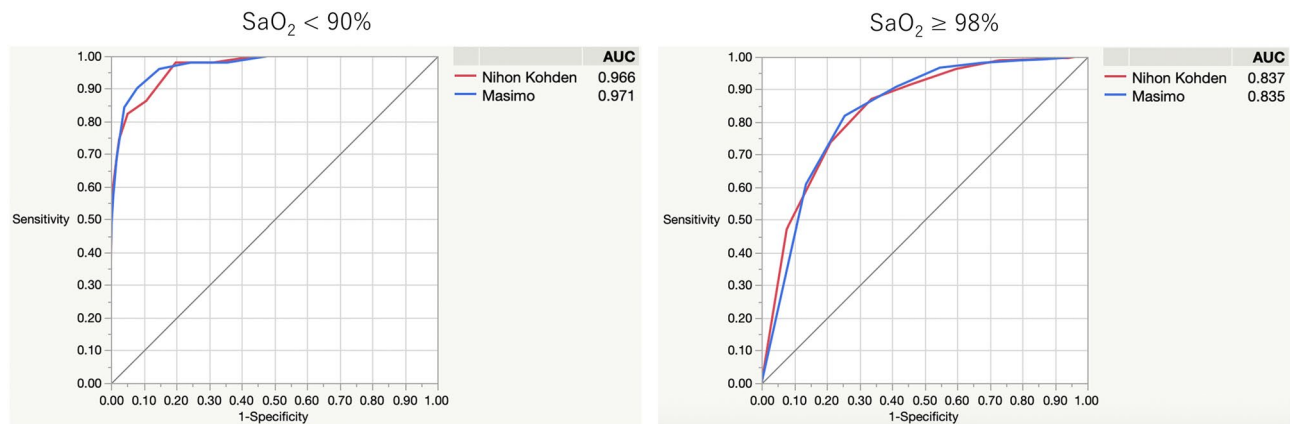
	Mean $\pm$ SD (95% CI)	P-value
<b><math>SaO_2 &lt; 94\%</math></b> (Blood gas analysis = 274)		
Nihon Kohden	1.41 $\pm$ 2.28% (1.14–1.68)	0.083
Masimo	1.74 $\pm$ 2.15% (1.49–2.00)	
<b><math>94\% \leq SaO_2 &lt; 98\%</math></b> (Blood gas analysis = 952)		
Nihon Kohden	0.57 $\pm$ 1.77% (0.46–0.69)	< 0.0001
Masimo	1.10 $\pm$ 1.60% (1.00–1.20)	
<b><math>SaO_2 \geq 98\%</math></b> (Blood gas analysis = 271)		
Nihon Kohden	0.51 $\pm$ 1.49% (0.33–0.69)	0.006
Masimo	0.84 $\pm$ 1.28% (0.68–0.99)	

**Table 3.** Differences in  $SpO_2$  measurements between pulse oximeters. *CI* confidence interval,  $SaO_2$  arterial oxygen saturation, *SD* standard deviation,  $SpO_2$  pulse-oximetric oxygen saturation.

## Discussion

In this study, we found that Nihon Kohden  $SpO_2$  measurements presented a lower bias than did Masimo  $SpO_2$  measurements compared with the actual  $SaO_2$ . The precision and correlation coefficients of  $SpO_2$  measurements were similar in both devices; specifically, these trends were seen in the " $SaO_2 \geq 94\%$ " group. In the low  $SpO_2$  group, there were no significant differences between  $SpO_2$  values measured by both devices.

Pulse oximeters indicate the calculated oxygen saturation values using the transmitted light signals of an LED irradiated on body. The theoretical formula for determining  $SpO_2$  from transmitted light signals has not been established, and each manufacturer uses its own formula. Therefore, the accuracy of  $SpO_2$  includes two factors: the validity of the formula and deviation from the formula. Also, pulse oximeters should detect the pulsation of arterial blood, but when the other pulsatile noises such as body movement are detected, it might be cause



**Figure 4.** AUC comparison between Nihon Kohden SpO<sub>2</sub> and Masimo SpO<sub>2</sub> for patients with SaO<sub>2</sub> < 90% and SaO<sub>2</sub> ≥ 98%. The blue line represents Masimo SpO<sub>2</sub> measurements, and the red line represents Nihon Kohden SpO<sub>2</sub>. The vertical axis represents true positive rate calculated by sensitivity, and the horizontal axis represents false positive rate calculated by (1—specificity). To detect SaO<sub>2</sub> < 90%, the area under the receiver operating characteristic curves (AUCs) were 0.966 using the Nihon Kohden and 0.971 using the Masimo monitor. When cut off point was set at SpO<sub>2</sub> 90% in Nihon Kohden and Masimo, its sensitivity and specificity were 62.8% and 99.0% in Nihon Kohden SpO<sub>2</sub>, and 56.9% and 99.3% in Masimo SpO<sub>2</sub>, respectively. There was no statistically significant difference in the AUCs between both monitors ( $P=0.530$ ). Regarding SaO<sub>2</sub> ≥ 98%, the AUCs were 0.837 using the Nihon Kohden and 0.835 using the Masimo monitor. When cut off point was set at SpO<sub>2</sub> 98% in Nihon Kohden and Masimo, its sensitivity and specificity were 87.1% and 66.2% in Nihon Kohden SpO<sub>2</sub>, and 90.8% and 58.7% in Masimo SpO<sub>2</sub>, respectively. However, there was no statistically significant difference in the AUCs of both monitors ( $P=0.841$ ). AUC, receiver operating characteristic curve.

erroneous calculation. To reduce these noises, each manufacturer uses its own original technology. The results of this study might be influenced by these technological differences between Nihon Kohden and Masimo SpO<sub>2</sub>.

To safely perform automatic control of a closed-loop ventilation system, it is essential to collect high-quality data continuously. When using the current INTELLiVENT-ASV, two types of SpO<sub>2</sub> measuring devices are now available: the Masimo and the Nihon Kohden. A previous study reported that Masimo SpO<sub>2</sub> measurements tended to overestimate SaO<sub>2</sub> compared to Nihon Kohden measurements<sup>15</sup>. In this study, although the precisions of both devices were similar, Masimo SpO<sub>2</sub> measurements were higher than Nihon Kohden SpO<sub>2</sub> measurements. Specifically, Masimo SpO<sub>2</sub> measurements were significantly different for SaO<sub>2</sub> readings > 94%. These results suggest we should be more cautious regarding overestimation of SaO<sub>2</sub> when using the Masimo SpO<sub>2</sub> readings. In this regard, using the Nihon Kohden SpO<sub>2</sub> monitor may be preferable with INTELLiVENT-ASV. On the other hand, the SpO<sub>2</sub> measured by Nihon Kohden often showed a difference of -3% or more compared to actual SaO<sub>2</sub> and the difference was larger than Masimo. It should be interpreted cautiously that the likelihood of misdetermination of hyperoxemia as normal was higher than that of Masimo.

At the low SpO<sub>2</sub> range (SpO<sub>2</sub> < 94%), the difference between devices was not statistically significant; concerning hypoxaemia detection, each pulse oximeter presented relatively high AUC values without a significant difference. According to a previous study, there was no significant difference between Nihon Kohden and Masimo SpO<sub>2</sub> measurements in the range of 85% < SpO<sub>2</sub> ≤ 90%<sup>15</sup>. Our result is similar; although, the relatively small number of analyses in our study might have influenced this result. In this study, both devices presented high SpO<sub>2</sub> compared with actual SaO<sub>2</sub>. In clinical settings, it is important to check the actual SaO<sub>2</sub> when SpO<sub>2</sub> presented higher than expected. Also, there was a difference that Masimo's equipment had true positive rate of 90% or more when false positive rate is 10%, but Nihon Kohden has a false positive rate of 15% to raise true positive rate to 90%. The small number of this group ( $n=51$ ) might partly be affected on this result. Because we usually control SpO<sub>2</sub> over 90% in critically ill patients, the number of blood gas analyses was relatively small compared with another group. Further examination is needed to evaluate this results in critically ill patients.

It is important to mount SpO<sub>2</sub> sensors correctly, especially in an ICU setting. A previous study evaluated four types of pulse oximeters that could accurately detect low perfusion during motion<sup>16</sup>. Motion impaired the performance of all four oximeters at all ranges, with lesser accuracies observed at the lower SaO<sub>2</sub> range. In contrast, at a lower perfusion, only the Nihon Kohden SpO<sub>2</sub> measurements remained accurate. In addition, when the probe was not symmetrically placed, SpO<sub>2</sub> measurements were inaccurate without an abnormal SpO<sub>2</sub> waveform; this phenomenon is called the “penumbra effect”<sup>17</sup>. To avoid this problem, we selected a seal-type sensor for all patients in this study.

This study has several limitations. First, it was a single-center observational study. All patients evaluated were Asian, except for one American. Because the accuracy of a pulse oximeter is affected by race<sup>18</sup>, further studies are warranted. Second, the mean SaO<sub>2</sub> values were in the optimal range ( $95.7 \pm 2.9\%$ ); SaO<sub>2</sub> values were distributed at higher levels with respect to hypoxaemia. Thus, it might be difficult to evaluate the accuracy of these monitors in the low SaO<sub>2</sub> range group. Furthermore, we did not measure the quality and perfusion indexes of the Masimo SpO<sub>2</sub> measurements, which might have affected these results. However, we recorded these data when the

SpO<sub>2</sub> value was stable. Third, although we defined the outlier as a difference of  $\geq 10\%$  in SpO<sub>2</sub> and SaO<sub>2</sub> values, its validation was unclear. However, we re-analysed the set of raw data, including these outliers, and found that the results were not affected by the exclusion of outliers. Fourth, we did not evaluate the Masimo SpO<sub>2</sub> measurements without mounting it on the G5. In this study, it was difficult to mount both SpO<sub>2</sub> sensors on the G5 simultaneously. However, the mechanics of each SpO<sub>2</sub> sensor were almost the same, with or without mounting on the G5. Finally, we could not evaluate continuously whether SpO<sub>2</sub> sensors were mounted correctly. Specifically, we did not consider the perfusion index of the Masimo. Also, we did not consider the presence of covariates, such as age, gender, and/or diseases. Further studies are needed to evaluate accuracy based on probe attachment.

Despite these limitations, this study also has several strengths. First, this is the first prospective observational study evaluating the bias and precision of pulse oximeters in critically ill mechanically ventilated patients with Hamilton ventilator. In addition, we evaluated the oxygenation status with respect to SpO<sub>2</sub>  $\geq 98\%$  and SpO<sub>2</sub>  $< 90\%$ . To keep SaO<sub>2</sub> strictly in the recommended range, it might be better to use Nihon Kohden SpO<sub>2</sub> measurements due to the smaller bias compared to the Masimo SpO<sub>2</sub> measurements.

## Conclusions

We found that Nihon Kohden SpO<sub>2</sub> measurements presented lower bias than Masimo SpO<sub>2</sub> measurements compared with the actual SaO<sub>2</sub>. The precision of SpO<sub>2</sub> measurements was relatively similar with both devices. This study suggests that when using INTELLiVENT-ASV and selecting automatic control of oxygenation in mechanically ventilated patients, it is preferable to use Nihon Kohden SpO<sub>2</sub> monitoring.

## Methods

**Study design and setting.** This was a single-center, prospective, observational study conducted in the general ICU of a university hospital (Tochigi, Japan) from June 2017 to November 2018 (UMIN000027671). Patients who were ventilated with a G5 ventilator (Hamilton Medical AG, Switzerland) in the ICU were included in this study. Clinical decisions, including changing ventilation mode, were made at the discretion of the attending ICU physicians. The study protocol was approved by the Institutional Research Ethics Committee of Jichi Medical University Hospital (A18-110). Written informed consent was obtained from each participant or nearest relative when the patient was incapacitated or unconscious. All methods were performed in accordance with the relevant guidelines and regulations.

**Participants.** Patients were eligible for enrolment if they were  $\geq 20$  years old and ventilated with a G5 during their ICU stay. The exclusion criteria were age  $< 20$  years, quality index of Nihon Kohden SpO<sub>2</sub>  $\leq 60\%$ , an unstable value of SpO<sub>2</sub> due to change in F<sub>I</sub>O<sub>2</sub> just before the blood sample was drawn, lack of SpO<sub>2</sub> data, and a history of management with veno-arterial extracorporeal membrane oxygenation. In addition, patients with a difference of  $> 10\%$  in SpO<sub>2</sub> and SaO<sub>2</sub> values were excluded due to the possibility of outliers. For validation purposes, we added the analysis of the raw data, including data of the possible outliers.

Patient baseline characteristics, including age, sex, height, body weight, body mass index, disease classification, and the use of veno-venous extracorporeal membrane oxygenation, were collected from electronic medical records. In addition, the results of blood gas analyses, including pH, PaO<sub>2</sub>, arterial carbon dioxide tension, haemoglobin, and SaO<sub>2</sub> values, were recorded. Furthermore, the PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ratio and severity of hypoxaemia were determined. Underlying medical histories were obtained, including information on hypertension, ischaemic heart disease, chronic heart failure, chronic obstructive pulmonary disease, cerebrovascular accidents, diabetes mellitus, and chronic kidney disease requiring haemodialysis. The Acute Physiology and Chronic Health Evaluation II<sup>19</sup> was used to assess organ dysfunction. ICU stays and mechanical ventilation durations were evaluated. In addition, ICU and hospital mortality rates were assessed.

**Pulse oximeter and blood gas analysis measurements.** SpO<sub>2</sub> was simultaneously measured by the TL-271T3 (Nihon Kohden, Tokyo, Japan) attached to Hamilton G5 ventilator, and by the RD SET™ NEO (Masimo, Irvine, CA, USA). Seal-type sensor probes were used and attached on the same side of the patient's hand. We replaced the sensors at least three times a day, and the sensors were replaced at the same time during study periods. The selection of fingers to use in sensor replacement was dependent on the bedside nurse's decision. The number of blood drawings or blood gases analyses were recorded and the SaO<sub>2</sub> and SpO<sub>2</sub> were compared. The timing of blood gas analyses was at the physician's discretion. Blood samples were immediately transferred and analysed by the RAPIDLAB1265 (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) or the ABL800 FLEX device (Radiometer Medical ApS, Denmark).

**Statistical analysis.** The relationship between measured SaO<sub>2</sub> and SpO<sub>2</sub> was evaluated using a Bland–Altman plot. Bias was calculated as the difference between SpO<sub>2</sub> and the actual SaO<sub>2</sub> from each pulse oximeter. Precision was determined from the standard deviation of the calculated bias. The bias and precision of the differences between SpO<sub>2</sub> and SaO<sub>2</sub>, upper and lower limits of agreement, and mean values of SpO<sub>2</sub> were calculated using bootstrapping methods. Resampling was randomly done with replacement up to 10,000 repetitions.

The ability to detect SaO<sub>2</sub>  $\geq 98\%$  was assessed using an AUC because SpO<sub>2</sub> 97% is default upper range of SpO<sub>2</sub> on INTELLiVENT-ASV<sup>20</sup>. The ability to detect SaO<sub>2</sub>  $< 90\%$  was also assessed using an AUC to detect hypoxemia.

To evaluate the differences in oxygenation, we established three categories of SaO<sub>2</sub> ranges (SaO<sub>2</sub>  $< 94\%$ ,  $94\% \leq \text{SaO}_2 < 98\%$ , and SaO<sub>2</sub>  $\geq 98\%$ ). Among these groups, differences between SpO<sub>2</sub> and SaO<sub>2</sub> were evaluated using the student's *t*-test. All analyses were performed using JMP 15 pro (SAS Institute Inc., Cary, NC, USA). Data are presented as means  $\pm$  standard deviations (SD) or as percentages where appropriate. *P*-values  $< 0.05$  were considered statistically significant.

**Prior presentations.** We presented prelimited data of this article at the European Society of Intensive Care Medicine 31st Annual Congress in Paris, France, 17 August 2018.

Received: 12 June 2020; Accepted: 15 April 2021

Published online: 26 April 2021

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## Acknowledgements

We acknowledge the assistance of the intensive care nursing staff at Jichi Medical University Hospital, Tochigi, Japan.

## Author contributions

S.K. collected the data, interpreted the statistical results, and wrote the first draft of this manuscript. S.N. contributed to the protocol design and revised the manuscript. K.K., K.T., and J.S. revised the manuscript. All authors are accountable for all aspects of the work, and all authors read and approved the final manuscript.

## Funding

This study was funded by internal departmental funds, Jichi Medical University School of Medicine.

## Competing interests

S.K. has a contract of consultation with Hamilton Medical. To conduct this study, a ventilator G5 from Nihon Kohden was rented to our ICU with the research contract. K.T, J.S, K.K, and S.N have disclosed that they do not have any potential conflicts of interest.

## Additional information

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1038/s41598-021-88608-7>.

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