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IMPROVED ACCURACY OF CARDIAC OUTPUT ESTIMATION BY THE PARTIAL CO_2 REBREATHING METHOD

Yoshifumi Kotake, MD[1], Takashige Yamada, MD[2], Hiromasa Nagata, MD[2], Takeshi Suzuki, MD[2], Ryohei Serita, MD[2], Nobuyuki Katori, MD[2], Junzo Takeda, MD[2] and Hideyuki Shimizu, MD[3]

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ABSTRACT. Objective. This study investigated the accuracy of the NICO monitor equipped with the newer software. Additionally, the effects of the increased dead space produced by the NICO monitor on ventilatory settings were investigated. **Methods.** Forty-two patients undergoing elective aortic reconstruction participated in this prospective, observational study at a university hospital. Cardiac output was continuously monitored using both the NICO monitor and continuous cardiac output (CCO) measured by a pulmonary artery catheter. A NICO monitor equipped with ver. 4.2 software was used for the first 21 patients while a NICO monitor equipped with ver. 5.0 software was used for the rest of the patients. Cardiac output measured by bolus thermodilution (BCO) at 30 min intervals was used as a reference. **Results.** The bias ± precision of the NICO monitor was 0.18 ± 0.88 l/min with ver. 4.2 software (n = 182) and 0.18 ± 0.83 l/min with 5.0 software (n = 194). The accuracy of the NICO monitor is comparable to CCO, whose bias ± precision against BCO is 0.19 ± 0.81 l/min (n = 376). At the same level of CO_2 production and minute ventilation, $PaCO_2$ was lower in the patients monitored by NICO with ver. 5.0 software than patients with ver. 4.2 software. **Conclusions.** This study demonstrated the improved performance of the NICO monitor with updated software. The performance of the NICO monitor with ver. 4.2 or later software is similar to CCO. However, the cardiac output measurement did not fulfill the criteria of interchangeability to the cardiac output measurement by bolus thermodilution. Updates to ver. 5.0 attenuated the effects of rebreathing introduced by the NICO monitor without compromising the accuracy of the cardiac output measurement.

KEY WORDS. cardiac output, monitor, partial CO_2 rebreathing, NICO, pulmonary artery catheter, aortic reconstruction.

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From the [1]Department of Anesthesiology, Toho University, 6-11-1, Ohmori-Nishi, Ohta, Tokyo 143-8541, Japan; [2]Department of Anesthesiology, School of Medicine, Keio University, Tokyo, Japan; [3]Department of Cardiovascular Surgery, School of Medicine, Keio University, Tokyo, Japan.

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Address correspondence to Y. Kotake, Department of Anesthesiology, Toho University, 6-11-1, Ohmori-Nishi, Ohta, Tokyo 143-8541, Japan.
E-mail: ykotake@med.toho-u.ac.jp

INTRODUCTION

The non-invasive cardiac output (NICO; Respironics-Novametrics, Wallingford, CT) monitor is one of the less-invasive cardiac output monitors and employs the indirect Fick partial CO_2 rebreathing method while also measuring pulmonary capillary blood flow (PCBF) [1, 2]. This device is characterized as minimally invasive for intubated, mechanically ventilated patients and is easy to setup with operator-independent performance. Although the basic principles are scientifically justified, this monitor uses a relatively complex algorithm and several assumptions. Previous reports, including ours, have demonstrated the larger bias of the NICO monitor compared to the thermodilution method [3–14]. Furthermore, a simulation study has revealed that the NICO method is relatively accurate when PCBF is between 3 and 6 l/min but that PCBF and cardiac output (CO) are overestimated below this range and underestimated above this range [15]. The manufacturer has been constantly updating the device software, but the accuracy of this device has not been extensively reviewed after these updates [16]. Application of the NICO monitor inevitably increases dead space and results in CO_2 accumulation. To alleviate CO_2 retention, the rebreathing cycle was reduced from 50 to 35 s with ver. 4.5 or later software. However, the impact of this possible improvement has not been reported.

The purpose of this prospective, observational study was to re-evaluate the accuracy of the NICO monitor equipped with next generation software in comparison with conventional bolus thermodilution in patients undergoing elective aortic reconstruction. Additionally, the effects of the shorter rebreathing time accompanied by the newer software on ventilatory settings were investigated.

METHODS AND MATERIALS

Following institutional review board approval, 42 patients undergoing elective aortic reconstruction for infrarenal abdominal aortic aneurysm were enrolled in this study after obtaining their informed consent. The study protocol is based on our previous report [9]. Anesthetic management was standardized in all patients as follows; after epidural catheterization at the Th 10/11 or 11/12 interspace, general anesthesia was induced with intravenous fentanyl and propofol and maintained with sevoflurane inhalation with or without nitrous oxide. Patients were paralyzed with vecuronium and mechanically ventilated with either the AS/3 ADU (Datex-Ohmeda, Helsinki, Finland) or KION (Siemens, Solna, Sweden) anesthesia machine. Tidal volume and respiratory rate were initially set at 10 ml/kg and 10 bpm, respectively, and were adjusted to maintain $PaCO_2$ at between 35 and 45 mmHg. Fluid administration, blood transfusion, epidural injection of local anesthetics, administration of inotropic and vasodilatory drugs, and other anesthetic management procedures were at the discretion of the attending anesthesiologist. An 8F pulmonary artery catheter (746HF8, Edwards Lifesciences, Irvine, CA) was inserted via the right internal jugular vein. Continuous cardiac output (CCO) and mixed venous oxygen saturation was continuously monitored with the Vigilance monitor (Edwards Lifesciences, Irvine, CA). These data were downloaded to a computer every 30 s for subsequent analysis.

These patients were divided into two groups according to the time of enrollment. Second generation software (software ver. 4.2) was used for the first 21 patients. In the other 21 patients, cardiac output was monitored with the same device updated with the newer software (software ver. 5.0). The NICO sensor was placed between the endotracheal tube and the heat and moisture exchanger (Hygrobac S, DAR-Mallinckrodt, Mirandola, Italy). Meticulous attention was paid to maintain adequate rebreathing circuit volume during monitoring. Data including average-mode cardiac output (CO-a), fast-mode cardiac output (CO-f), *PCBF*, CO_2 production (VCO_2), minute ventilation (MV) and end-tidal PCO_2 ($PetCO_2$) were downloaded to a computer every 3 min. CO-a was used for the evaluation of CO.

Bolus thermodilution cardiac output (BCO) measurements were made every 30 min after stable CCO and NICO measurements were obtained. Blood gas data were input to the NICO monitor prior to each BCO measurement to allow for the precise estimations of shunt fraction and NICO values. The injection of ice-cold saline was repeated four times within 3 min, and averaged data were used for analysis. The BCO measurements were included in the analysis only if the stability of hemodynamic status was achieved. Hemodynamic stability was arbitrarily defined as there being no fluid challenge or change in pharmacological intervention at least for 5 min. Non-shunted pulmonary blood flow was calculated with the following formula; non-shunted pulmonary blood flow = BCO × (1-shunt fraction). Shunt fraction (Qs/Qt) was calculated from the following formula: Qs/Qt = $CcO_2–CaO_2/CcO_2–CvO_2$ (CcO_2: end-pulmonary capillary oxygen content, CaO_2: arterial oxygen content, CvO_2: mixed venous oxygen content) [17]. CvO_2 was calculated using SvO_2 data obtained from PAC.

Data are expressed as mean ± SD and were statistically analyzed using the Prism software (ver. 4, Graphpad, San Diego, CA). Correlations and linear regression between either CCO or NICO against BCO were determined. A Bland–Altman analysis was used to compare the bias (the mean of the differences) and precision (standard deviation of bias) of NICO and CCO against BCO. Since multiple measurements were employed in each subject, modifications were used in calculating precision and the limits of agreement [18, 19]. The interchangeability between either CCO or NICO against BCO was defined as percentage error at the mean value of CO within 28% or relative error less than ±20% in more than 75% of measurement pairs [20]. Percentage error (expressed in %) was defined as 100 × 2 SD of the difference/mean value of

CO, and the relative error of each measurement pair (expressed in %) was defined as 100 × ([either NICO or CCO–BCO]/BCO) [21]. The relationship between the range of CO and accuracy was evaluated. Each measurement pair was further divided into the following three groups: CO less than 3 l/min, CO between 3 and 6 l/min and CO more than 6 l/min. Bias ± precision was calculated in each group.

To investigate the effects of increased dead space produced by rebreathing on ventilatory settings, the relationship between VCO_2 and MV to maintain $PaCO_2$ between 35 and 45 mmHg was analyzed. In each patient, $PetCO_2$, minute volume (MV) and VCO_2 data throughout the study period were obtained from the NICO monitor and were averaged. The relationship between the averaged VCO_2 and MV was used as an indicator of dead space introduced by the NICO monitor.

RESULTS

Demographic and operative data of the study participants are summarized in Table 1. There were no statistical differences between the two study groups. One hundred eighty-two BCO measurements were performed in the ver. 4.2 group and 194 BCO measurements were performed in the ver. 5.0 group. Since the relationship between CCO and BCO was quite similar in both study groups, combined data from all the patients were used to calculate the relationship between CCO and BCO. The mean CO derived from CCO in these 376 occasions was 4.8 ± 1.5 l/min. The relationship between BCO and CCO was expressed as the following formula: CCO = 0.92 × BCO + 0.58 l/min. The bias and precision (1 SD of bias) of CCO against BCO was 0.19 ± 0.81 l/min. Thus, the percentage error of CCO was 33.4%. The averaged relative error was 5 ± 17%, and in 283 occasions (75.2%) the relative error was within ±20%.

Table 1. Patient demographics

	Patients with ver. 4.2 software (n = 21)	Patients with ver. 5.0 software (n = 21)
Age (years)	70 ± 7	72 ± 8
Gender (male/female)	21/0	18/3
Height (cm)	165 ± 6	163 ± 6
Weight (kg)	65 ± 9	61 ± 13
Op. time (min)	232 ± 50	268 ± 56
XC time (min)	55 ± 14	61 ± 18

Data are expressed as mean ± SD.

The mean CO derived from NICO ver. 4.2 and ver. 5.0 measurements was 5.2 ± 1.3 and 5.0 ± 1.4 l/min, respectively. NICO and BCO also significantly correlated, but the data derived from ver. 5.0 software was closer to the line of identity than the data from ver. 4.2 software (NICO = 0.71 × BCO + 1.62 l/min, R^2 = 0.65, $P < 0.01$ with ver. 4.2 software vs. NICO = 0.89 × BCO + 0.65 l/min, R^2 = 0.65, $P < 0.01$ with ver. 5.0 software) (Figures 1 and 2, respectively). Overall, the bias and precision of NICO against BCO was 0.18 ± 0.88 l/min with ver. 4.2 software and 0.18 ± 0.83 l/min with ver. 5.0 software (Figures 3 and 4, respectively). PCBF overestimated non-shunted pulmonary blood flow and Qs/Qt was underestimated by NICO monitor compared to the PAC-derived estimates of Qs/Qt. The difference was not significant between the ver. 4.2 software and ver. 5.0 software (data not shown). The percentage error of NICO ver. 4.2 and ver. 5.0 measurements was 33.4% and 33.2%, respectively. The relative error was 8 ± 23% with ver. 4.2 software and 5 ± 20% with ver. 5.0 software. With ver. 4.2 software, the relative error was within ±20% in 125 occasions (68%), while the relative error was within ±20% in 131 (67%) occasions with ver. 5.0 software. The percentage error, as well as the number of occasions in which the relative error was within ±20%, were not significantly different between the two groups. Table 2 summarizes the results of subgroup analysis of the accuracy according to the range of CO. Ver. 5.0 software was more accurate

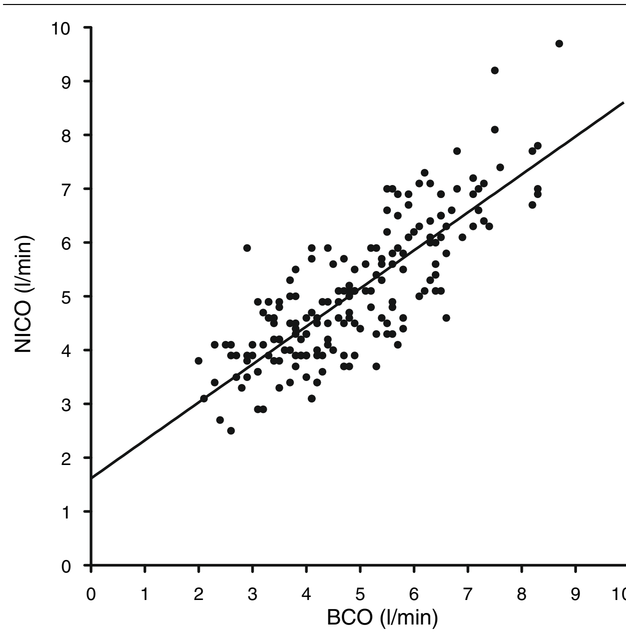

Fig. 1. Scatter plot of BCO and NICO monitor equipped with ver. 4.2 software (n = 182). Solid line demonstrates the regression line. R^2 = 0.65 ($P < 0.01$).

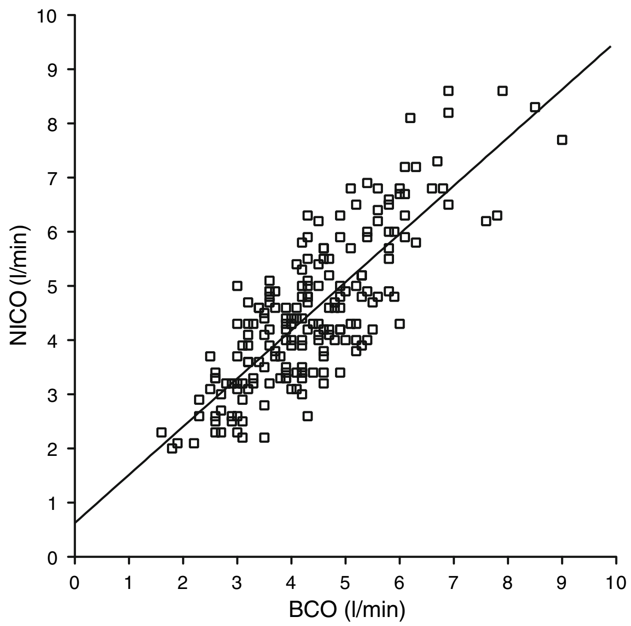

Fig. 2. Scatter plot of BCO and NICO monitor equipped with ver. 5.0 software (n = 194). Solid line demonstrates the regression line. $R^2 = 0.65$ *(*$P < 0.01$*).*

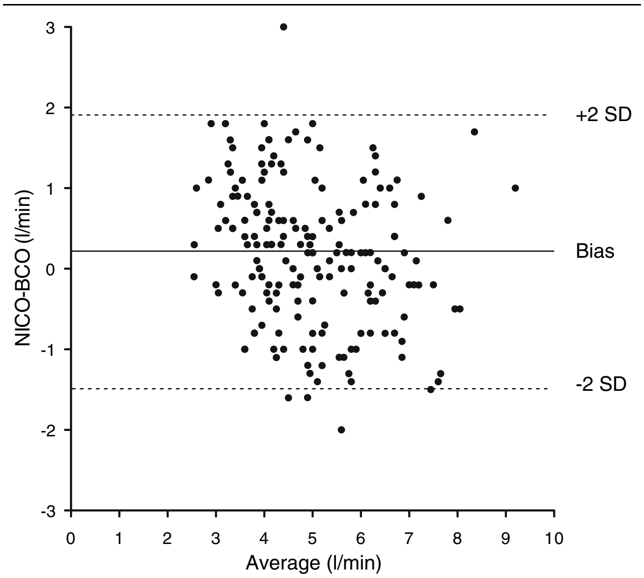

Fig. 3. Bland–Altman plot of the NICO monitor equipped with ver. 4.2 software against BCO (n = 182). Bias ± precision (1 SD of bias) = 0.18 ± 0.88 l/min. Dashed line indicates the limits of agreement (±2 SD of bias).

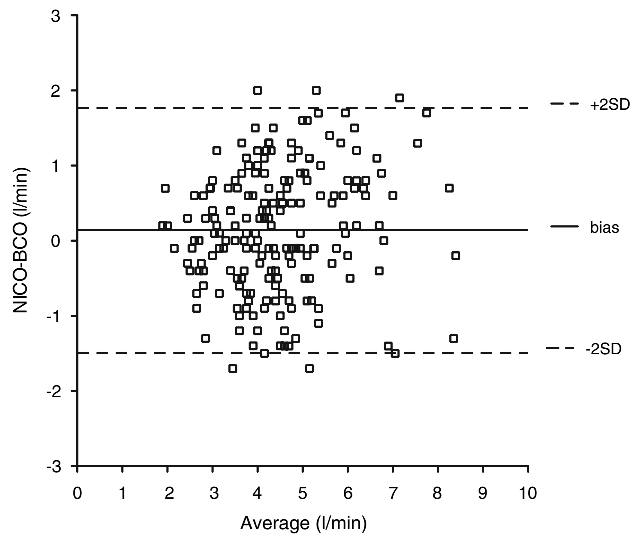

Fig. 4. Bland–Altman plot of the NICO monitor equipped with ver. 5.0 software against BCO (n = 194). Bias ± precision (1 SD of bias) = 0.18 ± 0.83 l/min. Dashed line indicates the limits of agreement (±2 SD of bias).

when the CO was in the range of 3–6 l/min, but a larger error was noted during high flow states with the ver. 5.0 software compared to the ver. 4.2 software (Figure 5).

The average VCO_2 during the measurement period was 128 ± 16 ml/min in patients measured with ver. 4.2 software and 122 ± 30 ml/min in patients measured with ver. 5.0 software. The average MV during mechanical ventilation was 6.23 ± 0.80 l/min in patients measured with ver. 4.2 software and 6.18 ± 0.82 l/min in patients measured with ver. 5.0 software. The average $PetCO_2$ was significantly lower in the second group compared to the first group (34.1 ± 3.1 mmHg vs. 36.6 ± 2.7 mmHg, $P = 0.023$). Figure 3 summarizes the relationship between the averaged VCO_2 and the averaged MV in each group. The slopes of these two correlations were significantly different between the two groups. These data suggest that the patients monitored with the NICO monitor equipped with ver. 5.0 software required smaller MV to achieve similar $PaCO_2$ levels when VCO_2 was relatively high.

DISCUSSION

This study demonstrated that the newer version of the NICO monitor was more accurate than previously reported. Furthermore, the shorter rebreathing time achieved with ver. 5.0 software resulted in the reduced need to increase MV during NICO application without compromising accuracy.

Several studies, including ours, have reported on the performance of the NICO monitor [3, 4, 6, 9, 10]. These

Table 2. Bias ± precision of each group based on the range of cardiac output

	With ver. 4.2 software	With ver. 5.0 software
CO < 3 l/min	−0.08 ± 0.26 (*n* = 4)	−0.29 ± 0.58 (*n* = 21)
CO between 3 and 6 l/min	0.20 ± 0.91 (*n* = 135)	0.10 ± 0.83 (*n* = 144)
CO > 6 l/min	0.14 ± 0.81 (*n* = 43)	0.67 ± 0.94 (*n* = 29)

Data are expressed as bias ± precision (1 SD of difference). *CO* cardiac output obtained with average mode of NICO (CO-a).

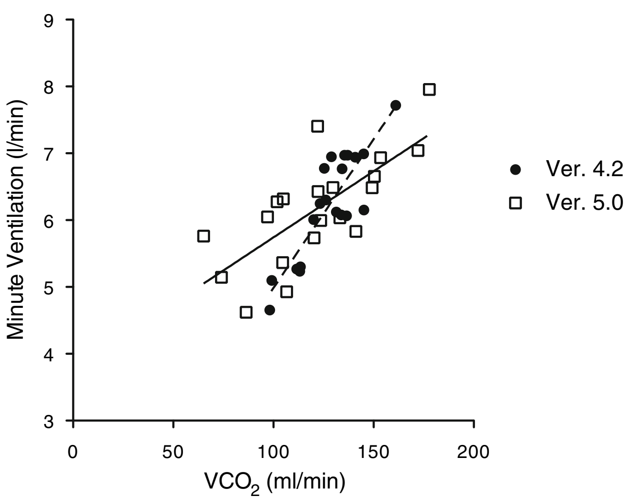

Fig. 5. Relationship between CO_2 production (VCO_2) and minute ventilation to maintain $PaCO_2$ between 35 and 45 mmHg. Closed circles denote subjects monitored with ver. 4.2 software while open squares denote subjects monitored with ver. 5.0 software. The dashed line and solid line represent the linear regression line of ver. 4.2 software and ver. 5.0 software, respectively.

studies employed earlier versions of the NICO monitor, and our study demonstrated that the bias ± precision of the NICO monitor with ver. 3.1 software was −0.58 ± 0.9 l/min. Most studies reported similar results and concluded that the NICO monitor demonstrated moderate accuracy. Inadequate rebreathing time, recirculation, the difference of CO_2 between alveolus and proximal airway as well as the difference between arterial and alveolar CO_2 have been attributed to modest accuracy [15]. However, investigations using newer software demonstrated better results. For example, Gueret et al. reported that the bias ± precision of the NICO monitor with ver. 4.2 software against continuous cardiac output monitoring (CCO) was −0.3 ± 1.1 l/min [16]. Considering the tendency of CCO to overestimate cardiac output, the bias between NICO and BCO might be smaller. But there are a limited number of studies that have addressed the performance of the NICO monitor with the updated software.

Another shortcoming of the NICO monitor is related to CO_2 rebreathing. Previous versions of the monitor use 50 s of rebreathing, and the $PaCO_2$ is expected to rise 3–5 mmHg due to rebreathing. Ver. 4.5 or later software reduces rebreathing time to 35 s. This change may attenuate CO_2 retention, but inadequate rebreathing times have been implicated in producing error in the CO_2 rebreathing method. However, the effects on the accuracy and $PaCO_2$ of the NICO monitor with newer software have not been systematically investigated.

Our data agree with the conclusion of the study employing the same software [16]. It is noteworthy that the tendency to underestimate CO found in previous studies was corrected with ver. 4.2 software and that the performance of NICO is quite similar to CCO. A simulation study revealed that the underestimation of NICO is mainly attributed to the assumption that CO_2 content in the mixed venous blood remains stable during rebreathing. Although it is not explicitly documented which part of the algorithm is modified in the software update, we speculate that some modification to estimate mixed venous CO_2 content was applied. Another potential source of error of NICO monitor derives from the estimation of shunted pulmonary blood flow. NICO monitor principally measures pulmonary capillary blood flow and estimates CO by adding estimated shunted blood flow. This is done by referring the blood gas data and established monogram. We found that the similar degree of overestimation of PCBF and underestimation of shunted pulmonary blood flow in both the software version. However, by examining the downloaded data, we found non-linear relationship between pulmonary capillary blood flow, CO-f and CO-a even in the stable conditions. This finding suggests that there may be complex averaging process to calculate PCBF and we could not draw firm conclusion about the contribution of shunt estimation on the accuracy of NICO monitor.

Our data demonstrated that the accuracy of ver. 4.2 and ver. 5.0 software was not significantly different despite the shorter rebreathing period. As discussed later, a shorter rebreathing period is surely beneficial to maintain adequate alveolar ventilation and CO_2 elimination. Thus the main advantage of ver. 5.0 software is to achieve a shorter rebreathing period without compromising accuracy. With ver. 5.0 software, the bias is clearly smaller when CO is between 3 and 6 l/min, while the bias is larger when CO is more than 6 l/min. Since the effect of recirculation is mainly responsible for the underestimation of CO by the CO_2 rebreathing method in a high flow state and a shorter rebreathing time may partially cancel the effect of recirculation, we hypothetize that the shorter rebreathing time may be somewhat responsible for the overestimation in high flow states seen with ver. 5.0 software.

Although we found a smaller bias $\pm$ precision compared to the previous version, it is still debatable whether the data from the NICO monitor can be interchangeable with the data from a PAC. Ideally, the limits of agreement (2 SD of difference) fall within 28% of the average CO to claim interchangeability [20]. Alternatively, the result is interchangeable if the difference between the two methods was within $\pm$20% in more than 75% of occasions [21]. In our study, CCO barely fulfilled the latter criteria, but NICO did not achieve this threshold. However, we believe the clinical usefulness of a hemodynamic monitor is not solely defined by its accuracy but that the balance between the data quality and invasiveness, continuity, applicability and operator-independency should also be considered. From this perspective, data from the current version of the NICO monitor may not be interchangeable with the data derived from a PAC, but a NICO monitor can still be used as a guide for hemodynamic management in patients undergoing aortic reconstruction.

One of the major changes between ver. 4.2 and ver. 5.0 software was decreasing the rebreathing time from 50 to 35 s. A shorter rebreathing time corresponds to decreased dead space and enables the maintenance of CO_2. As we have stated earlier, inadequate rebreathing time has been implicated in the inaccuracy of NICO monitors, and this shorter rebreathing time may increase the bias and precision. The effect of increased dead space by the application of a NICO monitor is attenuated with the ver. 5.0 software. The averaged $PaCO_2$ was lower in the patients monitored with ver. 5.0 software than those with ver. 4.2 software. Obviously, $PaCO_2$ is dictated by VCO_2, MV and dead space. We investigated the effects of additional dead space imposed by NICO monitoring by analyzing the relationship between VCO_2 and MV. The effect of increased dead space should be demonstrated with the increased ratio of MV against VCO_2. If this relationship is applicable, the NICO monitor with ver. 5.0 software adds less dead space compared to the ver. 4.2 monitor under the condition of increased VCO_2. This characteristic is particularly favorable to applying the NICO monitor to patients with ARDS, where limiting the tidal volume is crucial to prevent ventilator-induced lung injury and meticulous hemodynamic and fluid management are necessary. In conclusion, this study demonstrated the improved performance of the NICO monitor with the updated software and showed that the performance of the current version is similar to CCO. Additionally, the effect of rebreathing is attenuated in the ver. 5.0 software, due to the shortened rebreathing period and without negatively affecting accuracy.

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