Accuracy of carboxyhemoglobin dilution method for the measurement of circulating blood volume

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Purpose: The management of circulating blood volume (BVC) is crucial in intensive care unit (ICU) patients. The purpose of this study was to verify the accuracy and precision of the carbon monoxide-labeled hemoglobin (CO-Hb) dilution method (CO method) by comparing it with the ^{51}Cr -labeled erythrocyte dilution method (^{51}Cr method) for the measurement of BVC.

Methods: A prospective study was performed in 18 patients who underwent coronary artery bypass grafting (CABG) under mild hypothermic cardiopulmonary bypass (CPB). The BVC was measured by both the CO method and the ^{51}Cr method at 24 hr after ICU admission in order to verify the accuracy and precision of the CO method. Paired data were assessed in absolute terms, and percentage errors were calculated by the degree of agreement.

Results: Small mean differences and standard deviations between the CO method and the ^{51}Cr method (-70.2 ± 184.8 mL) and small percentage errors ($-0.49 \pm 1.29\%$) indicated the accuracy and precision of the CO method, and a close correlation was observed ($r=0.97$).

Conclusion: The CO method can measure BVC with a similar degree of accuracy as the ^{51}Cr method. It is simple, repeatable and safe without the risk of exposure to radioactivity in the ICU.

Objectif : La gestion du volume du sang circulant (VSc) est cruciale chez les patients des unités de soins intensifs (USI). Nous avons voulu vérifier, pour la détermination du VSc, la justesse et la précision de la méthode de dilution avec oxyde de carbone et hémoglobine marquée (méthode CO) en la comparant à la méthode avec des hématies marquées par le ^{51}Cr (méthode ^{51}Cr)

Méthode : Une étude prospective a été réalisée auprès de 18 patients qui subissaient un pontage aortocoronarien avec circulation extracorporelle (CEC) légèrement hypothermique. Le VSc a été mesuré selon les deux méthodes 24 h après l'admission à l'USI. Les données appariées ont été évaluées en valeur absolue et le pourcentage d'erreur a été calculé par le degré de concordance.

Résultats : De faibles différences moyennes et écarts types entre la méthode CO et la méthode ^{51}Cr ($-70,2 \pm 184,8$ mL) et de bas pourcentages d'erreur ($-0,49 \pm 1,29\%$) ont indiqué la justesse et la précision de la méthode CO, et une corrélation étroite a été observée ($r = 0,97$).

Conclusion : La méthode CO peut servir à mesurer le VSc avec un degré d'exactitude semblable à celui de la méthode ^{51}Cr . Elle est simple, répétable et sécuritaire, sans risque d'exposition à la radioactivité dans l'USI.

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ASSessment of circulating blood volume (BVC) is essential in the management of intensive care unit (ICU) patients. The BVC has been estimated by indirect means such as arterial blood pressure, heart rate, central venous pressure (CVP), or pulmonary capillary wedge pressure (PCWP), but these parameters do not correlate with values obtained by direct measurement.¹ Radioactive methods have been accepted as a reliable measurement for direct determination of BVC. However, such methods involve risk of exposure to radioactivity and, for this reason, repeated measurements are not available to ICU patients. The carbon monoxide-labeled hemoglobin (CO-Hb) dilution method (CO method) has been introduced for the measurement of BVC.^{2,3} The clinical usefulness of the CO method for BVC measurement was reported as both simple and safe with no risk of exposure to radioactivity.⁴ Obata *et al.*⁵ reported the highly predictive value of BVC measurement using the CO method in an animal hemorrhagic model. However, the CO method has not been widely accepted as a method for BVC measurement. In this study, we simultaneously measured BVC using the ⁵¹Cr method as well as the CO method and verified the accuracy and precision of the CO method by comparing the values obtained from the CO method with those obtained from the ⁵¹Cr method which is widely accepted as a standard method for BVC measurement.

Patients and methods

Patients

The protocol was approved by the Gunma University Ethical Committee for Human Research. A total of 18 patients (11 male, 7 female) who underwent coronary artery bypass grafting (CABG) and were admitted to the ICU of Gunma University Hospital from April 1997 to March 1998 were included in this study. The day before surgery, patients were fully informed of the purposes of the study and the procedures involved, and written consent was obtained.

Patients with 1) renal, hepatic or gastrointestinal disease, 2) left ventricular ejection fraction (LVEF) < 40%, as determined by preoperative echocardiography, 3) low cardiac output syndrome (LOS) with cardiac index < 2.5 L·min⁻¹·m⁻², 4) or postoperative bleeding > 500 mL for six hours after admission to the ICU were excluded from this study. Anesthesia was induced with 12-20 µg·kg⁻¹ fentanyl, 0.4-1.0 mg·kg⁻¹ midazolam and 0.1 mg·kg⁻¹ vecuronium and maintained by additional doses of fentanyl. Isoflurane (0.5-1.0%) was administered according to the hemodynamic response to surgical procedure. After induction of anesthesia, a

pulmonary artery catheter (744H-7.5 F; Baxter Healthcare Corp., Irvine, CA) was floated into the pulmonary artery via the right internal jugular vein for hemodynamic monitoring. Non-pulsatile, mild hypothermic cardiopulmonary bypass (CPB) was conducted in a standard manner using a membrane oxygenator including a heat exchanger (AFFINITY, AVECOR Cardiovascular Inc. Plymouth, MN) and roller pump (TOW NOK, Tonokura Ika Kogyo Co., Ltd., Tokyo, Japan). Rectal temperature was maintained at 28 to 30°C in all patients.

All patients were given a low dose of catecholamines ($\leq 3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine and $\leq 3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dobutamine, $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ diltiazem and $0.5\text{-}1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ nitroglycerin after surgery. No patients received blood transfusion but each received 476 ± 96 mL albumin 4% during the study period. In all patients, the endotracheal tubes were extubated 24 hr after ICU admission. The postoperative course was uneventful in all patients with no episodes of low cardiac output syndrome or major complications.

Measurement of BVC

The BVC was measured by the CO method at 24 hr after ICU admission. At 24 hr, BVC was also measured by the ⁵¹Cr method to verify the accuracy and precision of the CO method.

The CO method

After the baseline measurement of hemoglobin level (Hb_b) and CO-Hb concentration (CO-Hb_b), 100 mL blood was drawn from an arterial line into a sterile bag containing 15 mL of a citrate solution. Then, CO gas was insufflated into the bag through a bacterial filter. After insufflation and agitation three times, the oximeter indicated CO-Hb concentration (CO-Hb_i) > 97%, hemoglobin concentrations (Hb_i) were measured simultaneously and the indicator volume (V_i) of CO saturated blood was reinfused into a central vein. Two 1.0 mL arterial blood samples were drawn at 5, 10, 15, 20 and 30 min after reinfusion in order to measure CO-Hb concentration in the circulating blood. After the reinfusion of the indicator, several distinct dilution phases were observed: early circulation, a mixing phase and a major dilution phase.⁶ In this study, the major dilution phase was achieved within 5-10 min. Thus, we excluded the data at five minutes in our calculation. The mean CO-Hb concentration obtained from the two samples at each point were plotted on a semilogarithmic graph against time in minutes and the zero time value (CO-Hb_z) was obtained by the extrapolation of an exponential decay curve. Blood hemoglobin and CO-Hb concentrations were measured

with a blood gas analyzer with oximetry (ABL520, Radiometer, Copenhagen, Denmark). The PaO₂ values were controlled between 90 and 120 mmHg and the PaCO₂ between 35 and 45 mmHg in all patients. The BVc was calculated using the following equation;

$$\text{BVc (mL)} = V_f(\text{mL}) \times \text{Hb}_f/\text{Hb}_b (\text{g/dL}) \times \text{CO-Hb}_f / (\text{CO-Hb}_z - \text{CO-Hb}_b) (\%)$$

The ⁵¹Cr method

At 24 hr after ICU admission, BVc was measured by both the CO method and the ⁵¹Cr method to verify the accuracy and precision of the CO method. Blood volume was measured using the standard ⁵¹Cr method with modification.^{7,8} Initially, 20 mL of arterial blood was drawn using a heparin-coated syringe. Erythrocytes were collected by centrifugation and labelled with 100 µCi of [⁵¹Cr] sodium chromate (Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan) by incubation for 20 min at room temperature. After being centrifuged and washed in saline, the ⁵¹Cr-labelled erythrocytes were suspended in saline to create an original volume of 20 mL and the ⁵¹Cr radioactivity of the aliquot (100 µL) of this suspension was measured. Following injection of 20 mL ⁵¹Cr-labelled erythrocytes suspension, three samples of 0.5 mL arterial blood were drawn at 30 min for measurement of ⁵¹Cr radioactivity in the circulating blood, and the mean value was obtained.

Statistical analysis

The analysis of agreement was based on a method proposed by Bland and Altman⁹ for comparing two methods of evaluation of the same parameter. The differences between the CO method and the ⁵¹Cr method were plotted against the average of the two methods. Bias and precision were evaluated using the mean and standard deviation (SD) of the differences between the CO method and the ⁵¹Cr method. Bias measures systematic error between the methods, and precision quantifies the random error or variability. The limits of agreement were defined as the mean difference $\pm$ 2SD. To determine whether the differences between the methods depend on BVc in absolute terms, the percentage difference [$100 \times (\text{difference in BVc between the methods}) / (\text{mean of BVc by the two methods})$] was calculated and plotted against the average of the two methods.

Results

The characteristics of the patients, aortic cross-clamp and CPB time are shown in Table I and hemodynamic status before BVc measurement are shown in Table II.

TABLE I Patient characteristics and surgical data (mean $\pm$ SD (range))

n	18
Male/Female	11/7
Age (yr)	61.8 $\pm$ 6.2 (52 - 75)
Weight (kg)	50.5 $\pm$ 9.7 (37.3 - 70.3)
Body surface area (m ²)	1.49 $\pm$ 0.15 (1.24 - 1.84)
Cross-clamp time (min)	79.6 $\pm$ 16.4 (56 - 124)
CPB time (min)	109.2 $\pm$ 21.5 (78 - 158)

CPB = cardiopulmonary bypass

TABLE II Hemodynamic status before BVc measurement (mean $\pm$ SD)

HR	(beats·min ⁻¹)	91.3 $\pm$ 11.2
CI	(L·min ⁻¹ ·m ⁻²)	3.9 $\pm$ 0.7
MAP	(mmHg)	76.3 $\pm$ 11.9
MPAP	(mmHg)	17.2 $\pm$ 6.3
CVP	(mmHg)	5.2 $\pm$ 2.8
PCWP	(mmHg)	7.8 $\pm$ 3.1
PVRI	(dyne·sec·cm ⁻⁵ ·m ²)	168 $\pm$ 65
SVRI	(dyne·sec·cm ⁻⁵ ·m ²)	1436 $\pm$ 381

HR = heart rate; CI = cardiac index; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index

FIGURE 1 The BVc measurement with the CO method plotted against their simultaneous measurements with the ⁵¹Cr method.

Regression analysis revealed a correlation between values obtained from the CO and ⁵¹Cr method ($Y = 0.98X + 22.0$, $r = 0.97$) (Figure 1). As shown in Figure 2, the mean difference and standard deviations were: -70.2 ± 184.8 mL and percentage errors were $-0.49 \pm$

FIGURE 2 Difference in circulating blood volume measured by the CO method and the ^{51}Cr method ($\text{CO}-^{51}\text{Cr}$) plotted against their respective means. The horizontal lines indicate the mean and the mean ± 2 SD. Bias = -70.2 ± 184.8 mL (mean $\pm$ SD).

FIGURE 3 Percentage difference in circulating blood volume measured by the CO method and the ^{51}Cr method against their respective means.

Percentage difference = $100 \times (\text{CO}-^{51}\text{Cr}) / (\text{CO}+^{51}\text{Cr}) \times 0.5$. The horizontal lines indicate the mean and the mean ± 2 SD. Bias = $-0.49 \pm 1.29\%$ (mean $\pm$ SD).

1.29% (Figure 3). The CO-Hb concentration after the infusion of carbon monoxide saturated blood ranged from 2.1% to 5.0%. There was no sign of CO intoxication, such as headache and nausea, nor any major complications due to the reinfusion of blood, such as pulmonary infarction or infection.

Discussion

The ^{51}Cr method has been used as a standard method for the measurement of BVC.^{7,8} However, the ^{51}Cr method has several drawbacks in clinical use: 1) diffi-

culty in repeated measurement due to the long half-life (27.8 dy), 2) a risk of exposure to radioactivity and 3) a complicated measurement procedure. On the other hand, BVC measurement using the CO method is simple, repeatable and safe. The only equipment necessary for measurement is a CO-oximeter. Dissociation of carbon monoxide could be facilitated by the inhalation of pure oxygen. It is generally considered that CO-Hb concentration $< 10\%$ is harmless and causes no clinical symptoms,^{4,10} however, the highest CO-Hb concentration predicted $< 5\%$ in this study.

Nomof *et al.*⁷ reported that BVC measured using the CO-rebreathing method was 16% larger than with the ^{51}Cr method, as some CO was located in the extravascular space and some was excreted, metabolized or leaked. Christensen *et al.*¹¹ reported on the CO-rebreathing method using a to-and-fro system, and analysed CO kinetics using a computer simulation. They used a special system was designed by Water's Co. to avoid CO leakage. However, in our method, special instruments and computer analysis were not necessary.

Several methods for BVC measurement have been reported recently. Sugimoto *et al.*¹² reported a method for continuous measurement of BVC using ^{51}Cr in rats. Throughout their experiment there was no change in erythrocyte volume and therefore changes in blood volume were calculated continuously from changes in the radioactivity of ^{51}Cr in BVC. If there is bleeding, their method could not be used to calculate BVC. Hoeft *et al.*¹³ reported a different method for measuring blood volume using indocyanine green (ICG). However, blood ICG concentration is influenced by hepatic clearance, distribution of ICG, cardiac output and circulation time. A two-compartment model of circulation is required for an adequate fit of the data.

There are some disadvantages in using tracer dilution methods. Although the major dilution phase is achieved within 10 min in humans, it is prolonged by circulatory dysfunction.⁶ In this study, patients with low LVEF of $< 40\%$ by preoperative echocardiography and LOS with cardiac index of $< 2.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ after ICU admission were excluded. In patients with circulatory dysfunction, more frequent examination of CO-Hb concentration is required to confirm the achievement of the dilution phase. The CO method has several advantages over other methods because it requires only a brief time for labeling and allows rapid and repeated measurement with a CO-oximeter in the ICU. Further, the CO method avoids use of a radioactive tracer.

We verified the accuracy and precision of the CO method by the analysis of agreement proposed by Bland and Altman⁹ comparing the CO method with

the ^{51}Cr method. Our results showed a close relationship between values obtained by these two methods ($r = 0.97$). The difference in BVC measured by the two methods (bias) was -70.2 ± 184.8 mL and the percentage of errors were $-0.49 \pm 1.29\%$. Obata *et al.*⁵ reported the accuracy of the CO method in a rabbit hemorrhage model. Our study confirmed the accuracy and precision of the CO method in humans.

We conclude that the CO method can measure BVC with the same degree of accuracy as the ^{51}Cr method. There was no sign of CO intoxication, nor any major complications due to the reinfusion of blood. It is simple, repeatable and safe without the risk of exposure to radioactivity in the ICU.

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