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ORIGINAL RESEARCH

Comparison of the venous–arterial CO_2 to arterial–venous O_2 content difference ratio with the venous–arterial CO_2 gradient for the predictability of adverse outcomes after cardiac surgery

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Abstract

This study aimed to compare the prognostic performance of the ratio of mixed and central venous–arterial CO_2 tension difference to arterial–venous O_2 content difference (Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2, respectively) with that of the mixed and central venous-to-arterial carbon dioxide gradient (Pv-aCO_2 and Pcv-aCO_2, respectively) for adverse events after cardiac surgery. One hundred and ten patients undergoing cardiac surgery with cardiopulmonary bypass were enrolled. After catheter insertion, three blood samples were withdrawn simultaneously through arterial pressure, central venous, and pulmonary artery catheters, before and at the end of the operation, and preoperative and postoperative values were determined. The primary end-point was set as the incidence of postoperative major organ morbidity and mortality (MOMM). Receiver operating characteristic (ROC) curve and multivariate logistic regression analyses were performed to evaluate the prognostic reliability of Pv-aCO_2, Pcv-aCO_2, Pv-aCO_2/Ca-vO_2, and Pcv-aCO_2/Ca-cvO_2 for MOMM. MOMM events occurred in 25 patients (22.7%). ROC curve analysis revealed that both postoperative Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2 were significant predictors of MOMM. However, postoperative Pv-aCO_2 was the best predictor of MOMM (area under the curve [AUC]: 0.804; 95% confidence interval [CI] 0.688–0.921), at a 5.1-mmHg cut-off, sensitivity was 76.0%, and specificity was 74.1%. Multivariate analysis revealed that postoperative Pv-aCO_2 was an independent predictor of MOMM (odds ratio [OR]: 1.42, 95% CI 1.01–2.00, p = 0.046) and prolonged ICU stay (OR: 1.45, 95% CI 1.05–2.01, p = 0.024). Pv-aCO_2 at the end of cardiac surgery was a better predictor of postoperative complications than Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2.

Keywords Arterial–venous O_2 content · Cardiac surgery · Postoperative complication · Venous–arterial CO_2

1 Introduction

With advances in terms of the perioperative environment, including patient care and surgical techniques, the number of high-risk surgical patients has markedly increased [1, 2]. In these patients, maintaining adequate tissue perfusion and oxygenation can decrease postoperative adverse outcomes [3]. Cardiovascular surgery using cardiopulmonary bypass (CPB) can induce ischemic–reperfusion injury, due to decreased cardiac output (CO) and inadequate tissue perfusion. Accordingly, early identification of tissue hypoperfusion is crucial, as it may improve postoperative outcomes in cardiac surgical patients [4].

Central venous oxygen saturation (ScvO_2) and mixed venous oxygen saturation (SvO_2) have traditionally been used to predict the systemic oxygen supply–demand balance [5, 6]. Low ScvO_2 or SvO_2 may indicate inadequate tissue oxygen delivery (DO_2); however, these indices do not ensure adequate tissue perfusion in cases with normal or supra-normal values [7]. Additionally, normalization of these markers does not guarantee adequate tissue perfusion and may not lead to decreased organ dysfunction [8]. Therefore, additional markers of decreased DO_2 are needed. Recently, the mixed venous-to-arterial carbon dioxide gradient (Pv-aCO_2) and central venous-to-arterial carbon dioxide gradient (Pcv-aCO_2) have been suggested as complementary markers for identifying septic patients with inadequate DO_2 [9, 10]. Both

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of these variables have proven prognostic ability in high-risk surgical patients [11]. However, $Pv\text{-}aCO_2$ and $Pcv\text{-}aCO_2$ may increase without a decrease in DO_2, because of the Haldane effect [12]. Therefore, in addition to the CO_2 gradient, O_2 changes should be considered.

The ratio of carbon dioxide elimination (VCO_2) to oxygen consumption (VO_2) is a reliable index for predicting global anaerobic metabolism. Under anaerobic metabolic conditions, VCO_2 may exceed VO_2 [13]. According to the Fick principle, the ratio of the venous–arterial carbon dioxide content difference to the arterial–venous oxygen content difference ($Cv\text{-}aCO_2/Ca\text{-}vO_2$) is equal to VCO_2/VO_2. Within the physiological range, the correlation between the partial pressure of CO_2 (PCO_2) and CO_2 content is almost linear; thus, PCO_2 could be utilized as a substitute for CO_2 content [14]. The $Pv\text{-}aCO_2$ to arterial-to-mixed venous O_2 content difference ratio ($Pv\text{-}aCO_2/Ca\text{-}vO_2$) can be a reliable index for identifying inadequate DO_2 [13]. Recently, the utility of this ratio as a marker of resuscitation has been demonstrated, particularly in patients with septic shock [15]. Additionally, in septic patients, Mallat et al. [16] have shown that the ratio of the central venous–arterial CO_2 tension difference to arterial–central-venous O_2 content difference ($Pcv\text{-}aCO_2/Ca\text{-}cvO_2$) is a more reliable index of inadequate systemic tissue hypoxia than $ScvO_2$ and serum lactate level. However, in cardiac surgery patients, the prognostic power of $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ for postoperative outcomes is unclear.

We hypothesized that, in cardiac surgery, $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ may be better markers of global anaerobic metabolism than CO_2 gradient variables. To test our hypothesis, we compared the prognostic performance of $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ with that of $Pv\text{-}aCO_2$ and $Pcv\text{-}aCO_2$ for predicting adverse events after cardiac surgery.

2 Methods

2.1 Patients and anesthetic management

The current study protocol was approved by the institutional review board of our hospital. Written informed consent was obtained from all patients. Patients undergoing elective cardiac surgery using CPB were included in this study. The exclusion criteria were as follows: intra-cardiac shunts and renal failure requiring hemodialysis.

No premedication was given, and all enrolled patients could take clear liquids until 3 h preoperatively. Anesthesia induction was accomplished by bolus administration of midazolam (0.04–0.18 mg/kg), propofol (0.5–2 mg/kg), fentanyl (2–10 μg/kg), rocuronium (0.6–1.2 mg/kg), and inhalation agents (sevoflurane [0.5–3.0%] or desflurane [2.0–6.0%]). Following tracheal intubation, the arterial pressure catheter was inserted into the radial artery, and a central venous catheter (CVC), and pulmonary artery catheter (PAC) were placed into the right internal jugular vein. The positions of the CVC and PAC were confirmed by the pressure waveform and transesophageal echocardiography. Cardiac output and stroke volume were continuously measured by the PAC. Patients were ventilated with a tidal volume of 6–7 mL/kg (ideal body weight). The fraction of inspiratory oxygen was adjusted to maintain PaO_2 from 100 to 150 mmHg. Respiratory rate (normally 10–12 times/min) was controlled to keep $PaCO_2$ in the range of 35–40 mmHg. Anesthetic maintenance was performed using inhalation agents (sevoflurane [1.0–2.0%]) or (desflurane [3.0–6.0%]), remifentanil (0.1–0.4 μg/kg/min), fentanyl (10–40 μg/kg for the total dose). Rocuronium or vecuronium was administered for muscle relaxation, as appropriate. The depth of general anesthesia was adjusted by maintaining the bi-spectral index value (BIS monitor v4.0; Medtronic Inc, Minneapolis, MN, USA) in the range of 45–60.

2.2 Cardiopulmonary bypass management and postoperative course

During the CPB procedure, propofol (2–6 mg/kg/h) was continuously infused for general anesthesia maintenance. Standard CPB management was provided with a flow rate around 2.5 L/min/m^2 and mean arterial pressure between 50 and 75 mmHg. The $PaCO_2$ value was adjusted from 40 to 45 mmHg by alpha-stat management. Hematocrit level was maintained at around 20%. For cardiac arrest, mild hypothermia (rectal temperature 32 °C) was induced, and standard antegrade and retrograde crystalloid was administered for myocardial protection. When performing circulation arrest, deep hypothermia was performed (rectal temperature around 26 °C), and selective cerebral perfusion was provided (flow rate: 500 mL/min, mean arterial pressure in the right radial artery: 40–50 mmHg). Intra-aortic balloon pumping (IABP) was used when circulatory failure (cardiac index less than 1.5 L/min/m^2 and systolic blood pressure less than 80 mmHg) continued even after massive infusion of inotropic drugs (the doses of dopamine + dobutamine > 10 μg/kg/min and norepinephrine > 0.1 μg/kg/min).

After surgery, all patients were transferred to the intensive care unit (ICU) while remaining intubated. Postoperative management was performed by cardiac surgeons blinded to the study protocol. All patients remained in the ICU at least until the first postoperative day and were discharged from the ICU when patient's state was stable. The criteria for ICU discharge were as follows: (1) hemodynamic stability was defined as the absence of arrhythmias requiring drug treatment, systolic blood pressure more than 100 mmHg, with less than two inotropic drugs, and urine output more than

1 mL/kg/h; (2) respiratory stability was defined as blood oxygen saturation more than 94% with an oxygen mask (< 5 L/min).

2.3 Blood gas measurements

After insertion of the pulmonary catheter, three blood samples were withdrawn simultaneously through the arterial pressure, central venous, and pulmonary artery catheters, and the samples were analyzed using an ABL800 (Radiometer Medical. Co., Ltd., Copenhagen, Denmark) to determine the following variables: arterial oxygen tension (PaO_2), arterial oxygen saturation (SaO_2), arterial carbon dioxide tension ($PaCO_2$), central venous oxygen tension ($PcvO_2$), central venous oxygen saturation ($ScvO_2$), central venous carbon dioxide tension ($PcvCO_2$), mixed venous oxygen tension (PvO_2), mixed venous oxygen saturation (SvO_2), mixed venous carbon dioxide tension ($PvCO_2$), and hemoglobin concentration (Hb). Pv-aCO_2, Pcv-aCO_2, Pv-aCO_2/Ca-vO_2, and Pcv-aCO_2/Ca-cvO_2 were calculated as follows:

$$CaO_2 = (1.34 \times SaO_2 \times Hb) + (0.003 \times PaO_2)$$

$$CcvO_2 = (1.34 \times ScvO_2 \times Hb) + (0.003 \times PcvO_2)$$

$$CvO_2 = (1.34 \times SvO_2 \times Hb) + (0.003 \times PvO_2)$$

$$Ca - cvO_2 = CaO_2 - CcvO_2$$

$$Ca - vO_2 = CaO_2 - CvO_2$$

$$Pcv - aCO_2 = PcvCO_2 - PaCO_2$$

$$Pv - aCO_2 = PvCO_2 - PaCO_2$$

$$Pv - aCO_2/Ca - vO_2 = (PvCO_2 - PaCO_2)/(CaO_2 - CvO_2)$$

$$Pcv - aCO_2/Ca - cvO_2 = (PcvCO_2 - PaCO_2)/(CaO_2 - CcvO_2)$$

Blood gas analysis was performed twice (before and at the end of the operation), in the same way, and Pv-aCO_2, Pcv-aCO_2, Pv-aCO_2/Ca-vO_2, and Pcv-aCO_2/Ca-cvO_2 were also calculated. The values before and at the end of the operation were recorded as the "preoperative" and "postoperative" values, respectively.

2.4 Statistical analysis

The primary end-point in the current study was set as the incidence of postoperative severe adverse events (major organ morbidity and mortality: MOMM), as previously described [17]. MOMM was determined as major complications (either life threatening or potentially resulting in permanent functional disability) from the Society of Thoracic Surgeons 30-day operative mortality and morbidity risk model. MOMM events were defined as follows: death, stroke requiring drug treatment, renal failure requiring dialysis, prolonged mechanical ventilation (more than 48 h postoperatively), re-operation, and deep sternal infection. We investigated the prognostic ability of Pv-aCO_2, Pcv-aCO_2, Pv-aCO_2/Ca-vO_2, and Pcv-aCO_2/Ca-cvO_2 for postoperative outcomes. The threshold value of 1.4 mmHg·dL/mL reported by Mekontso-Dessap et al. [13], was used to predict the presence of hyperlactatemia in critically ill patients, while the current study was conducted to predict postoperative adverse outcomes in cardiac surgery. To the best of our knowledge, there is no study to evaluate the threshold value of Pv-aCO_2/Ca-vO_2 for predicting postoperative adverse outcomes in cardiac surgery. Therefore, we used the threshold value of 1.0 mmHg·dL/mL for the calculation of sample size, because, generally, $VCO_2/VO_2 > 1.0$ suggests the presence of tissue hypoperfusion [14]. In a preliminary study (the data were personal and unpublished), Pv-aCO_2/Ca-vO_2 was higher than 1.0 mmHg·dL/mL in 3 of 15 patients evaluated (20.0%). Postoperative MOMM occurred in 33.3% of patients with Pv-aCO_2/Ca-vO_2 above the threshold of 1.0, and in 16.7% of patients below this threshold. A power analysis using this preliminary data indicated that a sample size of 100 subjects would be sufficient to detect a difference of 16.6% in the incidence of MOMM events between patients with higher or lower values of Pv-aCO_2/Ca-vO_2, with a power of 0.80 and alpha of 0.05. Considering a dropout rate of 10%, we therefore enrolled 110 patients.

Receiver operating characteristic (ROC) curves were constructed to evaluate the prognostic reliability of Pv-aCO_2, Pcv-aCO_2, Pv-aCO_2/Ca-vO_2., and Pcv-aCO_2/Ca-cvO_2 for predicting the incidence of postoperative MOMM, the results of which were expressed as the area under the curve (AUC) with 95% confidence intervals (95% CIs), as well as sensitivity and specificity for the optimal threshold. The method shown by Hanley and McNeil [18] was used to compare the AUCs in the ROC analysis. Multivariate logistic regression analyses were performed to investigate the independent effects of perioperative factors on the risk of developing postoperative MOMM and prolonged ICU length of stay, and the results were expressed as odds ratio (OR) with 95% CI. In the multivariate analysis, we included the perioperative factors with the p value less than 0.10 in the univariate analyses comparing patients "with and without postoperative MOMM" and "with and without ICU length of stay ≥ 3". Student's *t*-test and the Mann–Whitney U-test were used to compare perioperative continuous variables between patients with and without MOMM events. Categorical variables were compared with the χ^2 test or Fisher's exact test. Paired *t*-test and Wilcoxon's signed-rank test were used to compare metabolic status, body temperature, hemodynamic data, as well as CO_2 and O_2 derived parameters, between preoperative and postoperative periods. All results were expressed as mean ± standard deviation unless otherwise indicated. For all analyses, p-values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using StatFlex version 6.0 (Artech. Co., Ltd., Osaka, Japan).

3 Results

Of the 110 patients enrolled in this study, no patient was excluded. MOMM events occurred in 25 patients (22.7%) postoperatively. Tables 1 and 2 show the Baseline characteristics in patients with and without MOMM events

Table 1 Baseline characteristics in patients with and without MOMM

Variables	With MOMM (n = 25)	Without MOMM (n = 85)	p value
Gender (M/F)	13/12	41/44	0.741
Age (year)	75.2 ± 6.07	72.6 ± 9.53	0.357
Height (cm)	155 ± 11.7	156 ± 10.2	0.580
Weight (kg)	56.4 ± 15.5	55.0 ± 12.0	0.946
NYHA classification			0.016*
I/II	8/10	26/48	
III/IV	3/4	10/1	
EuroSCORE II	8.05 ± 9.67	3.57 ± 3.34	0.003*
Pre-anesthetic transthoracic echo findings			
Ejection Fraction (%)	50.0 ± 14.6	55.5 ± 10.5	0.238
E/e′	23.4 ± 12.5	19.1 ± 8.36	0.158
Respiratory function			
%VC (%)	90.3 ± 21.9	92.8 ± 19.3	0.713
$FEV_{1.0}$ (%)	70.9 ± 11.6	75.7 ± 9.27	0.156
Pre-anesthetic arterial blood gas analysis			
pH	7.42 ± 0.05	7.43 ± 0.04	0.356
Partial pressure of oxygen (mmHg)	91.0 ± 21.3	93.3 ± 18.4	0.719
Partial pressure of CO_2 (mmHg)	38.8 ± 6.53	38.7 ± 5.01	0.527
Base excess (mEq/L)	0.76 ± 3.08	1.31 ± 2.25	0.361
Medical history			
Hypertension, n (%)	15 (60%)	52 (61%)	0.916
Diabetes mellitus, n (%)	4 (16%)	14 (16%)	0.955
Atrial fibrillation	4 (16%)	16 (19%)	0.748
Asthma, n (%)	1 (4.0%)	6 (7.1%)	0.557
Chronic kidney disease, n (%)	14 (56%)	35 (41%)	0.190
Cerebral vascular disease, n (%)	6 (24%)	12 (14%)	0.240
Operation			0.663
CABG, n (%)	1 (4.0%)	11 (13%)	
AVR, n (%)	5 (20%)	18 (21%)	
Aorta replacement, n (%)	6 (24%)	24 (28%)	
CABG + AVR, n (%)	2 (8.0%)	5 (5.9%)	
CABG + MVR	3 (12%)	3 (3.5%)	
MVR, n (%)	6 (24%)	15 (18%)	
AVR + MVR, n (%)	2 (8.0%)	8 (9.4%)	
Myxoma extirpation, n (%)	0 (0.0%)	1 (1.2%)	

Data are expressed as mean ± SD

Chronic kidney disease: estimated glomerular filtration rate < 60 mL/min/1.73 m^2

MOMM major organ morbidity and mortality, *NYHA* New York Heart Association, *E* early diastolic left ventricular inflow velocity, *e′* early diastolic velocity of the mitral annulus, *%VC* percent vital capacity, *FEV1.0 (%)* forced expiratory volume in one second, *CO_2* carbon dioxide, *CABG* coronary artery bypass grafting, *AVR* aortic valve replacement, *MVR* mitral valve repair

*p < 0.05 statistically significant

Table 2 Baseline characteristics in patients with and without ICU length of stay ≥ 3 days

Variables	With ICU length of stay ≥ 3 days (n = 31)	Without ICU length of stay ≥ 3 days (n = 79)	p value
Gender (M/F)	14/17	42/37	0.450
Age (year)	74.9 ± 6.46	72.5 ± 9.65	0.371
Height (cm)	156 ± 11.3	156 ± 10.3	0.846
Weight (kg)	58.3 ± 15.6	54.2 ± 11.4	0.329
NYHA classification			
I/II	11/12	23/46	0.036*
III/IV	4/4	9/1	
EuroSCORE II	6.92 ± 8.98	3.67 ± 3.42	0.046*
Pre-anesthetic transthoracic echo findings			
Ejection fraction (%)	53.0 ± 13.0	54.7 ± 11.2	0.238
E/e′	23.3 ± 11.4	18.8 ± 8.47	0.064
Respiratory function			
%VC (%)	87.7 ± 25.2	94.1 ± 17.0	0.434
$FEV_{1.0}$ (%)	71.0 ± 8.24	75.9 ± 10.5	0.132
Pre-anesthetic arterial blood gas analysis			
pH	7.42 ± 0.04	7.43 ± 0.04	0.353
Partial pressure of oxygen (mmHg)	90.3 ± 19.9	93.7 ± 18.7	0.512
Partial pressure of CO_2 (mmHg)	38.5 ± 6.45	38.8 ± 4.91	0.794
Base excess (mEq/L)	0.59 ± 2.99	1.41 ± 2.19	0.142
Medical history			
Hypertension, n (%)	19 (61%)	48 (61%)	0.959
Diabetes mellitus, n (%)	6 (19%)	12 (15%)	0.595
Atrial fibrillation	6 (19%)	14 (18%)	0.842
Asthma, n (%)	2 (6.5%)	5 (6.3%)	0.981
Chronic kidney disease, n (%)	16 (52%)	33 (42%)	0.350
Cerebral vascular disease, n (%)	6 (19%)	12 (15%)	0.595
Operation			0.539
CABG, n (%)	4 (13%)	19 (24%)	
AVR, n (%)	1 (3.2%)	6 (7.6%)	
Aorta replacement, n (%)	8 (26%)	13 (17%)	
CABG + AVR, n (%)	3 (9.7%)	7 (8.9%)	
CABG + MVR	10 (32%)	20 (25%)	
MVR, n (%)	3 (9.7%)	3 (3.8%)	
AVR + MVR, n (%)	2 (6.5%)	10 (13%)	
Myxoma extirpation, n (%)	0 (0.0%)	1 (1.3%)	

Data are expressed as mean ± SD

Chronic kidney disease: estimated glomerular filtration rate < 60 mL/min/1.73 m^2

ICU intensive care unit, *NYHA* New York Heart Association, *E* early diastolic left ventricular inflow velocity, *e′* early diastolic velocity of the mitral annulus, *%VC* percent vital capacity, *FEV1.0 (%)* forced expiratory volume in one second, CO_2 carbon dioxide, *CABG* coronary artery bypass grafting, *AVR* aortic valve replacement, *MVR* mitral valve repair

*p < 0.05 statistically significant

and ICU length of stay ≥ 3 days. Patients with postoperative MOMM had higher New York Heart Association (NYHA) classifications and EuroScore II than those without MOMM (p = 0.016). Perioperative data in patients with and without MOMM and ICU length of stay ≥ 3 days are shown in Tables 7 and 3. Patients with postoperative MOMM had significantly longer operation time, and larger transfusion volume and blood loss than those without MOMM ($p < 0.05$). SvO_2 and $ScvO_2$ were not significantly different between the two groups. Although the preoperative lactate concentration was not significantly different, the postoperative value in the patients with MOMM was significantly higher than those without MOMM (p = 0.030). Patients with postoperative MOMM

Table 3 Perioperative data in patients with and without ICU length of stay ≥ 3 days

Variables	With ICU length of stay ≥ 3 days (n = 31)	Without ICU length of stay ≥ 3 days (n = 79)	p value
Operation time (min)	391 ± 101	311 ± 81.7	< 0.001*
CPB time (min)	199 ± 56.5	170 ± 58.7	0.019*
Clamp time (min)	149 ± 60.6	136 ± 51.9	0.297
Infusion (mL)	5461 ± 1925	4965 ± 1519	0.270
Transfusion (mL)	3564 ± 1732	2325 ± 1171	0.001*
Urine output (mL)	2641 ± 1332	2800 ± 1301	0.573
Blood loss (mL)	1634 ± 763	1102 ± 549	< 0.001*
Percentage of patients receiving catecholamines [average dosage]			
Dopamine (%, [mcg/kg/min])	83.9 [3.93 ± 1.73]	89.9 [3.28 ± 1.40]	0.440/0.339
Dobutamine (%, [mcg/kg/min])	16.1 [4.60 ± 2.19]	11.4 [3.50 ± 1.66]	0.503/0.449
Milrinone (%, [mcg/kg/min])	32.3 [0.25 ± 0.11]	12.7 [0.29 ± 0.11]	0.017*/0.028*
Norepinephrine (%, [mcg/kg/min])	32.3 [0.04 ± 0.02]	12.7 [0.03 ± 0.02]	0.017*/0.015*
Epinephrine (%, [mcg/kg/min])	6.5 [0.05 ± 0.007]	0 [0]	0.023*/0.024*
Arterial blood gas analysis			
Partial pressure of oxygen (preoperative) (mmHg)	228 ± 151†	195 ± 101†	0.707
Partial pressure of oxygen (postoperative) (mmHg)	142 ± 72.7†	148 ± 74.6†	0.401
Partial pressure of CO_2 (preoperative) (mmHg)	41.0 ± 4.0	41.2 ± 4.8†	0.918
Partial pressure of CO_2 (postoperative) (mmHg)	42.5 ± 6.0	42.5 ± 4.0†	0.511
Metabolic status and body temperature			
pH (preoperative)	7.40 ± 0.06	7.40 ± 0.05	0.814
pH (postoperative)	7.37 ± 0.06	7.39 ± 0.04	0.095
Base excess (preoperative) (mEq/L)	0.3 ± 3.1	0.2 ± 2.5	0.871
Base excess (postoperative) (mEq/L)	− 0.8 ± 2.9	0.4 ± 2.0	0.125
Lactate concentration (preoperative) (mmol/L)	1.0 ± 0.9†	0.9 ± 0.6†	0.845
Lactate concentration (postoperative) (mmol/L)	2.9 ± 1.5†	2.3 ± 1.0†	0.076
Body temperature (preoperative) (°C)	36.4 ± 0.6†	36.4 ± 0.6†	0.842
Body temperature (postoperative) (°C)	35.9 ± 0.8†	36.0 ± 0.5†	0.472
Hemodynamic data			
Mean arterial pressure (preoperative) (mmHg)	77.1 ± 15.2†	74.1 ± 12.0†	0.335
Mean arterial pressure (postoperative) (mmHg)	67.8 ± 8.54†	70.1 ± 9.93†	0.222
Central venous pressure (preoperative) (mmHg)	9.97 ± 3.88†	8.66 ± 4.06†	0.128
Central venous pressure (postoperative) (mmHg)	12.1 ± 3.67†	10.5 ± 3.50†	0.036*
Stroke volume (preoperative) (mL)	50.4 ± 17.1	49.7 ± 15.7	0.887
Stroke volume (postoperative) (mL)	46.2 ± 18.8	48.9 ± 15.9	0.569
Continuous cardiac output (preoperative) (L/min)	3.23 ± 0.77	3.54 ± 1.03	0.379
Continuous cardiac output (postoperative) (L/min)	3.74 ± 0.97	3.99 ± 1.30	0.631
CO_2 and O_2 derived parameters			
SvO_2 (preoperative) (%)	74.6 ± 9.18†	76.1 ± 5.48†	0.298
SvO_2 (postoperative) (%)	69.8 ± 8.82†	74.0 ± 8.10†	0.026*
$ScvO_2$ (preoperative) (%)	76.8 ± 8.99	78.3 ± 6.77†	0.366
$ScvO_2$ (postoperative) (%)	73.4 ± 8.79	75.4 ± 7.97†	0.271
$Pv\text{-}aCO_2$ (preoperative) (mmHg)	5.82 ± 3.12†	5.12 ± 2.19†	0.431
$Pv\text{-}aCO_2$ (postoperative) (mmHg)	7.73 ± 3.90†	4.02 ± 1.94†	< 0.001*
$Pcv\text{-}aCO_2$ (preoperative) (mmHg)	7.45 ± 3.18	6.21 ± 3.04†	0.207
$Pcv\text{-}aCO_2$ (postoperative) (mmHg)	8.51 ± 4.05	5.92 ± 2.34†	< 0.001*
$Ca\text{-}vO_2$ (preoperative) (mL/dL)	4.08 ± 1.03	3.87 ± 0.92	0.107
$Ca\text{-}vO_2$ (postoperative) (mL/dL)	4.08 ± 1.17	3.75 ± 1.01	0.076
$Ca\text{-}cvO_2$ (preoperative) (mL/dL)	3.78 ± 1.13	3.64 ± 1.00	0.378
$Ca\text{-}cvO_2$ (postoperative) (mL/dL)	3.70 ± 1.17	3.62 ± 1.21	0.434

Table 3 (continued)

Variables	With ICU length of stay ≥ 3 days (n = 31)	Without ICU length of stay ≥ 3 days (n = 79)	p value
$Ca\text{-}vO_2 \times CO$ (preoperative) (mL/min)	118 ± 42.9	144 ± 57.7	0.115
$Ca\text{-}vO_2 \times CO$ (postoperative) (mL/min)	142 ± 54.9	156 ± 66.0	0.539
$Ca\text{-}cvO_2 \times CO$ (preoperative) (mL/min)	106 ± 42.8	137 ± 54.6	0.042*
$Ca\text{-}cvO_2 \times CO$ (postoperative) (mL/min)	129 ± 47.2	153 ± 76.0	0.309
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (preoperative) (mmHg·dL/mL)	1.59 ± 1.10	1.41 ± 0.88†	0.485
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (postoperative) (mmHg·dL/mL)	2.20 ± 1.79	1.09 ± 0.51†	< 0.001*
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (preoperative) (mmHg·dL/mL)	2.25 ± 1.50	1.82 ± 0.99	0.410
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (postoperative) (mmHg·dL/mL)	2.59 ± 1.70	1.74 ± 0.83	0.012*

Data are expressed as mean ± SD

ICU intensive care unit, *CPB* cardiopulmonary bypass, *SvO_2* mixed venous oxygen saturation, *$ScvO_2$* Central venous oxygen saturation, *$Pv\text{-}aCO_2$* mixed venous-to-arterial carbon dioxide gradient, *$Pcv\text{-}aCO_2$* central venous-to-arterial carbon dioxide gradient, *$Ca\text{-}vO_2$* arterial-mixed venous O_2 content difference, *$Ca\text{-}cvO_2$* arterial-central venous O_2 content difference, *CCO* continuous cardiac output, *$Pv\text{-}aCO_2/Ca\text{-}vO_2$* mixed venous–arterial carbon dioxide gradient to arterial-mixed venous O_2 content difference ratio, *$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$* central venous–arterial carbon dioxide gradient to arterial–central venous O_2 content difference ratio

*$p < 0.05$ statistically significant (between 2 groups), †$p < 0.05$ statistically significant (preoperative vs. postoperative)

had significantly lower postoperative mean arterial pressure ($p = 0.012$). Cardiac index and stroke volume were not significantly different between the patients with and without MOMM. However, the patients with MOMM were more likely to receive the inotropic support using epinephrine, norepinephrine and milrinone compared to those without MOMM. In terms of CO_2- and O_2-derived parameters, postoperative $Pv\text{-}aCO_2$, $Pcv\text{-}aCO_2$, $Pv\text{-}aCO_2/Ca\text{-}vO_2$, and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ values were significantly higher in patients with MOMM than in those without MOMM, while no significant difference was noted regarding preoperative values.

Figure 1a, b reveal ROC curve analyses for the prognostic ability for MOMM events of $Pv\text{-}aCO_2$- and $Pcv\text{-}aCO_2$-related variables, respectively. Both postoperative $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ were significant predictors of the incidence of postoperative MOMM (AUC: 0.780 [95% CI 0.663–0.897] and AUC: 0.688 [95% CI 0.543–0.834]) (Table 4). The AUCs of postoperative $Pv\text{-}aCO_2$ and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ were significantly higher than the preoperative values, respectively ($Pv\text{-}aCO_2$: $p = 0.003$, $Pv\text{-}aCO_2/Ca\text{-}vO_2$: $p = 0.009$) (Fig. 1a). Postoperative $Pcv\text{-}aCO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ had a higher (but not significant) AUC than preoperative values, respectively ($Pcv\text{-}aCO_2$: $p = 0.084$, $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$: $p = 0.079$) (Fig. 1b). Additionally, postoperative $Pv\text{-}aCO_2$ was the best predictor for the incidence of postoperative MOMM (AUC: 0.804 [95% CI 0.688–0.921], cut-off value: 5.1 mmHg, sensitivity: 76.0%, specificity: 74.1%).

Tables 5 and 6 reveal the results of multivariate analysis for postoperative MOMM and prolonged ICU length of stay (more than or equal to 3 days). Postoperative $Pv\text{-}aCO_2$ was an independent predictor of both MOMM (OR: 1.42, 95% CI 1.01–2.00, $p = 0.046$) (Table 5) and prolonged ICU length of stay (OR: 1.45, 95% CI 1.05–2.01, $p = 0.024$) (Table 6), whereas the postoperative lactate concentration was not.

4 Discussion

To the best of our knowledge, this is the first study to evaluate the prognostic ability of $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ for postoperative adverse outcomes in cardiac surgery. Patients with MOMM had a larger increase in postoperative $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ values. Additionally, ROC analysis revealed that postoperative $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ had adequate power to predict postoperative severe complications. Postoperative $Pv\text{-}aCO_2$ demonstrated better predictive ability than $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$. Although the sensitivity and specificity derived from the ROC analysis were not so good, multivariate analyses revealed that postoperative $Pv\text{-}aCO_2$ was the best predictor of postoperative outcomes.

The values of $Pv\text{-}aCO_2/Ca\text{-}vCa\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ can be used as reliable markers of global anaerobic metabolism, which is based on the ratio of CO_2 production to VO_2 in the whole body. $Pv\text{-}aCO_2$ and $Pcv\text{-}aCO_2$ are accepted complementary markers for identifying patients with inadequate DO_2 [9, 10]. Both of these variables have demonstrated prognostic ability in patients with shock status [11, 19]. Furthermore, by also considering O_2 changes, given by the arterial–venous O_2 gradient, the accuracy and precision of this concept can be increased. The ratio of VCO_2/VO_2 is a reliable index for assessing global anaerobic metabolism. Recent studies have shown that $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ could be a surrogate for

Table 4 Areas under the ROC curves for predicting postoperative MOMM

Factor	AUC	95% CI	Cut off value	Sensitivity (%)	Specificity (%)	Youden index	P value versus $Pv\text{-}aCO_2$ (postoperative)	P value versus $Pv\text{-}aCO_2/Ca\text{-}vO_2$ (postoperative)
SvO_2 (preoperative) (%)	0.513	0.364–0.661	76.8	44.0	43.5	−0.12	<0.001*	0.005*
SvO_2 (postoperative) (%)	0.608	0.468–0.748	71.7	60.0	60.0	0.20	0.034*	0.064
$ScvO_2$ (preoperative) (%)	0.541	0.413–0.670	78.5	52.0	51.8	0.04	0.003*	0.007*
$ScvO_2$ (postoperative) (%)	0.518	0.382–0.654	75.5	48.0	48.2	−0.04	0.002*	<0.001*
Lactate concentration (preoperative) (mmol/L)	0.524	0.383–0.665	0.7	52.0	51.8	0.04	<0.001*	0.006*
Lactate concentration (postoperative) (mmol/L)	0.615	0.485–0.745	2.2	60.0	58.8	0.19	0.005*	0.064
$Pv\text{-}aCO_2$ (preoperative) (mmHg)	0.537	0.401–0.674	5.3	52.0	51.8	0.04	0.003*	0.008*
$Pv\text{-}aCO_2$ (postoperative) (mmHg)	0.804	0.688–0.921	5.1	76.0	74.1	0.50	–	0.773
$Pcv\text{-}aCO_2$ (preoperative) (mmHg)	0.559	0.424–0.693	6.7	52.0	54.1	0.06	0.007*	0.015*
$Pcv\text{-}aCO_2$ (postoperative) (mmHg)	0.731	0.588–0.874	6.8	72.0	70.6	0.43	0.435	0.602
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (preoperative) (mmHg dL/mL)	0.536	0.394–0.678	1.3	52.0	51.8	0.04	0.004*	0.009*
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (postoperative) (mmHg dL/mL)	0.780	0.663–0.897	1.3	64.0	71.8	0.36	0.773	–
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (preoperative) (mmHg dL/mL)	0.506	0.364–0.649	1.8	52.0	51.8	0.04	0.001*	0.004*
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (postoperative) (mmHg dL/mL)	0.688	0.543–0.834	1.8	68.0	69.4	0.37	0.220	0.332

Youden index = (sensitivity + specificity) − 1

ROC receiver operating characteristic, *MOMM* major organ morbidity and mortality, *AUC* area under curve, *CI* confidence interval, SvO_2 mixed venous oxygen saturation, $ScvO_2$ central venous oxygen saturation, $Pv\text{-}aCO_2$ mixed venous-to-arterial carbon dioxide gradient, $Pcv\text{-}aCO_2$ central venous-to-arterial carbon dioxide gradient, $Pv\text{-}aCO_2/Ca\text{-}vO_2$ mixed venous–arterial carbon dioxide gradient to arterial-mixed venous O_2 content difference ratio, $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ central venous-arterial carbon dioxide gradient to arterial–central venous O_2 content difference ratio

VCO_2/VO_2 and may be useful for evaluating global anaerobic metabolism [13, 16, 20–22]. Furthermore, some previous studies have suggested that these ratios respond to the changes in global tissue oxygenation faster than blood lactate concentration [15, 16]. Lactate concentration may not be able to track the changes in tissue perfusion rapidly, which could be the reason why the blood lactate concentration was not an independent predictor of postoperative outcomes in the present study. In our study, the ROC analysis showed that postoperative $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ can predict poor outcomes after cardiac surgery, with AUCs of 0.780 and 0.688, respectively. The cut-off values of $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (1.3 and 1.8 mmHg·dL/mL, respectively) for predicting postoperative MOMM in our study was highly similar to that in previous studies. However, postoperative $Pv\text{-}aCO_2$ demonstrated better predictive ability than $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$. Additionally, multivariate analysis revealed that postoperative $Pv\text{-}aCO_2$, but not $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$, was an independent predictor of both MOMM and prolonged ICU length of stay.

The possible reasons for the superior ability of $Pv\text{-}aCO_2$ for predicting postoperative outcomes as compared to $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ may be as follows.

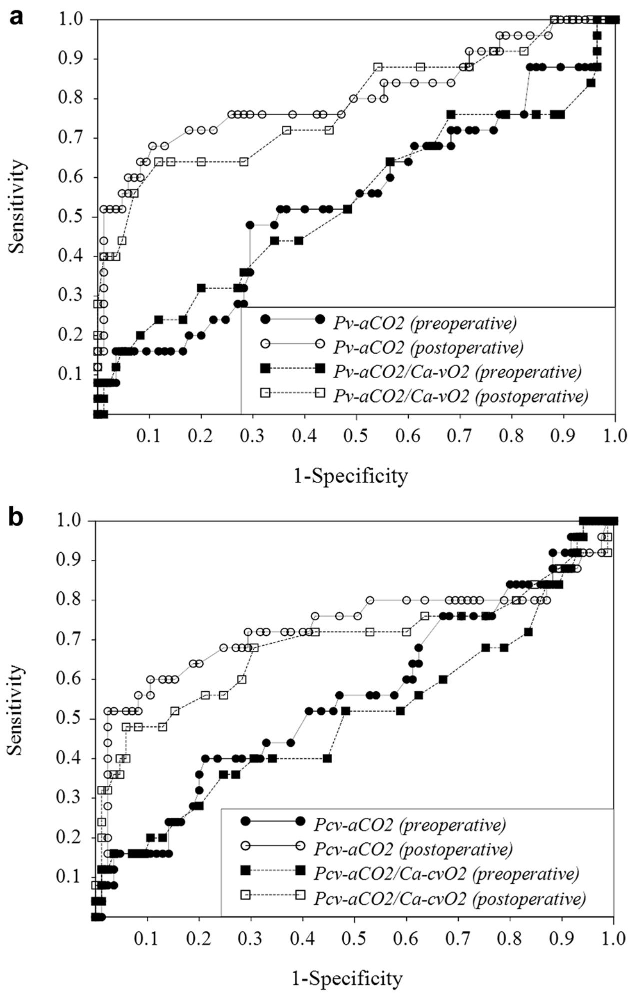

Fig. 1 Receiver operating characteristic (ROC) curve analyses for evaluating the prognostic reliability of the mixed and central venous–arterial CO_2 tension difference to arterial–venous O_2 content difference ratio (Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2, respectively) and the mixed and central venous-to-arterial carbon dioxide gradient (Pv-aCO_2 and Pcv-aCO_2, respectively) for predicting the incidence of postoperative major organ morbidity and mortality. **a** Mixed venous-related variables (Pv-aCO_2 and Pv-aCO_2/Ca-vO_2), **b** central venous-related variables (Pcv-aCO_2 and Pcv-aCO_2/Ca-cvO_2). Filled circle: preoperative Pv-aCO_2 and Pcv-aCO_2, open circle: postoperative Pv-aCO_2 and Pcv-aCO_2, filled box: preoperative Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2, open box: postoperative Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2

First, Pv-aCO_2/Ca-vO_2 is not equivalent to Cv-aCO_2/Ca-vO_2. Calculation of Cv-aCO_2 is complicated, whereas Pv-aCO_2 is easily calculated. The relationship between Cv-aCO_2 and Pv-aCO_2 is almost linear under normal conditions, but becomes non-linear when Pv-aCO_2 is abnormal [23]. Haldane effect facilitates the binding of CO_2 to hemoglobin at lower O_2 saturation, and the relationship between CO_2 content and CO_2 tension is affected by O_2 saturation and acidosis [24]. In anaerobic conditions, tissue acidosis and hypoxia frequently occur, and the discrepancy between Cv-aCO_2 and Pv-aCO_2

Table 5 Multivariate logistic regression model for MOMM: N = 110; incidence of MOMM = 25 (22.7%)

Factor	Odds ratio	95% CI	p value
EuroSCORE II	1.14	0.99–1.31	0.080
CPB time	1.02	0.89–1.17	0.768
Transfusion	1.01	0.94–1.09	0.785
Blood loss	1.03	0.88–1.21	0.707
Mean arterial pressure (postoperative)	0.96	0.89–1.04	0.294
pH (postoperative)	2.34	0.33–16.8	0.396
Base excess (postoperative)	0.69	0.43–1.10	0.119
Lactate concentration (postoperative)	1.07	0.64–1.79	0.793
Pv-aCO_2 (postoperative)	1.42	1.01–2.00	0.046*
Pv-aCO_2/Ca-vO_2 (postoperative)	1.55	0.50–4.80	0.451

Odds ratio is based on 10 min change in operation time and CPB time, 100 mL change in transfusion and blood loss, and 0.1 change in pH

MOMM major organ morbidity and mortality, *CI* confidence interval, *CPB* cardiopulmonary bypass, *Pv-aCO_2* mixed venous-to-arterial carbon dioxide gradient, *Pv-aCO_2/Ca-vO_2* mixed venous-arterial carbon dioxide gradient to arterial-mixed venous O_2 content difference ratio

*$p < 0.05$ statistically significant

Table 6 Multivariate logistic regression model for ICU length of stay ≥ 3 days: N = 110; incidence of ICU length of stay ≥ 3 days = 32 (29.1%)

Factor	Odds ratio	95% CI	p value
EuroSCORE II	1.03	0.88–1.20	0.728
E/e′ (preanesthetic)	1.02	0.95–1.11	0.573
CPB time	0.97	0.85–1.10	0.603
Transfusion	1.00	0.92–1.08	0.958
Blood loss	1.13	0.94–1.36	0.190
Central venous pressure (postoperative)	1.06	0.87–1.27	0.572
pH (postoperative)	0.30	0.07–1.22	0.092
Lactate concentration (postoperative)	1.08	0.63–1.85	0.771
Pv-aCO_2 (postoperative)	1.45	1.05–2.01	0.024*
Pv-aCO_2/Ca-vO_2 (postoperative)	1.37	0.63–2.97	0.431

Odds ratio is based on 10 min change in operation time and CPB time, 100 mL change in transfusion and blood loss, and 0.1 change in pH

ICU intensive care unit, *CI* confidence interval, *E* early diastolic left ventricular inflow velocity, *e′* early diastolic velocity of the mitral annulus, *CPB* cardiopulmonary bypass, *Pv-aCO_2* mixed venous-to-arterial carbon dioxide gradient, *Pv-aCO_2/Ca-vO_2* mixed venous-arterial carbon dioxide gradient to arterial-mixed venous O_2 content difference ratio

*$p < 0.05$ statistically significant

increases due to the Haldane effect. Similarly, the value of Pv-aCO_2/Ca-vO_2 should be equal to Cv-aCO_2/Ca-vO_2 under normal conditions, but is greatly affected by the Haldane effect, and thus, its interchangeability to Cv-aCO_2/Ca-vO_2 may be doubtful under anaerobic conditions [25]. Although the physiology of Cv-aCO_2/Ca-vO_2 is robust, Pv-aCO_2/Ca-vO_2 may not detect anaerobic conditions in some cases. Ospina-Tascon et al. found that Cv-aCO_2/Ca-vO_2 was significantly associated with mortality in septic shock patients, whereas Pv-aCO_2/Ca-vO_2 was not [15]. Second, calculating VCO_2 according to Fick's principle is valid under stable conditions. However, the recovery of blood-flow after tissue ischemia can lead to overestimation of VCO_2 and increases in VCO_2/VO_2. In such cases, the value of Pv-aCO_2/Ca-vO_2 may not be valid for predicting patients' outcomes. Third, pseudo-normalization of Pv-aCO_2/Ca-vO_2 could occur under conditions of high oxygen consumption. A CO increase can cause a decrease in Ca-vO_2 if VO_2 is maintained constant under anaerobic conditions. Therefore, the pseudo-normalization of Pv-aCO_2/Ca-vO_2 may not occur under high CO conditions combined with reduced or constant VO_2 [26]. However, pseudo-normalization of Pv-aCO_2/Ca-vO_2 could occur under conditions of high VO_2 and high CO. The results revealed that the values of continuous CO and VO_2 (both Ca-v$O_2 \times$CO and Ca-cv$O_2 \times$CO) were not high in the current study (Tables 7, 3). Therefore, the third possible reason may not be applicable in the current study.

In the current study, mixed venous-related variables (Pv-aCO_2 and Pv-aCO_2/Ca-vO_2) had better predictive ability than central venous-related variables (Pcv-aCO_2 and Pcv-aCO_2/Ca-cvO_2). The equivalence between mixed venous-related variables and central venous-related variables has not been proven, although relatively good agreement between Pv-aCO_2 and Pcv-aCO_2 has been demonstrated [27]. However, as indicated in a previous study, the CO distribution changes in patients with hemodynamic collapse [28]. During hemodynamic instability, blood-flow to the abdominal organs is reduced while that to vital organs, including brain and heart, is maintained [28]. Therefore, the discrepancy between Pv-aCO_2 and Pcv-aCO_2 may increase during periods of hemodynamic instability. In previous studies [29, 30], it has been shown that the venous–arterial difference in CO_2 tension could not predict postoperative complications. However, in these studies, venous blood gas measurement was performed from the central venous catheter. As shown in the current study, mixed venous-related variables should be used to predict postoperative outcomes in cardiac surgery patients.

The current study had some methodological limitations. First, blood gas measurement was not performed during the postoperative period. The Pv-aCO_2 value in the postoperative period may have more reliability for detecting postoperative complications than that during surgery. Second, patients who underwent circulatory arrest and cerebral perfusion were enrolled in the current study. This may have affected the results of blood gas measurement, and some postoperative complications, including infectious disease and stroke. Third, postoperative body temperature was significantly lower than preoperative value, which can affect blood/gas solubility coefficient. However, postoperative temperature was in almost normal range both for the patients with and without MOMM, and did not significantly differ between these two groups. Therefore, the difference between pre- and postoperative temperature did not affect the results. Even with these limitations, the results of the present study suggest that clinicians may be able to predict postoperative complications in cardiac surgery patients by measuring Pv-aCO_2 values at the end of surgery.

5 Conclusions

In the current study, we demonstrated that Pv-aCO_2 at the end of surgery had superior ability for predicting postoperative complications than Pv-aCO_2/Ca-vO_2 and Pcv-aCO_2/Ca-cvO_2. Pv-aCO_2 at the end of surgery is an independent risk factor for postoperative complications, such as prolonged ICU length of stay and MOMM. Thus, it would be possible that the incidence and severity of postoperative complications can be predicted by measuring the value of Pv-aCO_2 at the end of surgery.

Table 7 Perioperative data in patients with and without MOMM

Variables	With MOMM (n = 25)	Without MOMM (n = 85)	p value
Operation time (min)	396 ± 110	316 ± 81.1	< 0.001*
CPB time (min)	198 ± 64.4	173 ± 56.9	0.061
Clamp time (min)	144 ± 67.7	138 ± 50.5	0.640
Infusion (mL)	5592 ± 2077	4961 ± 1486	0.225
Transfusion (mL)	3610 ± 1884	2399 ± 1184	0.013*
Urine output (mL)	2536 ± 1399	2819 ± 1279	0.342
Blood loss (mL)	1640 ± 840	1138 ± 550	0.004*
Percentage of patients receiving catecholamines [average dosage]			
Dopamine (%, [mcg/kg/min])	76.0 [4.07 ± 1.10]	91.8 [3.30 ± 1.57]	0.032*/0.459
Dobutamine (%, [mcg/kg/min])	20.0 [5.00 ± 1.41]	10.6 [3.28 ± 1.86]	0.215/0.166
Milrinone (%, [mcg/kg/min])	36.0 [0.24 ± 0.12]	12.9 [0.30 ± 0.10]	0.009*/0.018*
Norepinephrine (%, [mcg/kg/min])	36.0 [0.04 ± 0.02]	12.9 [0.03 ± 0.02]	0.009*/0.010*
Epinephrine (%, [mcg/kg/min])	8.0 [0.05 ± 0.007]	0 [0]	0.009*/0.009*
Arterial blood gas analysis			
Partial pressure of oxygen (preoperative) (mmHg)	205 ± 137	204 ± 112†	0.281
Partial pressure of oxygen (postoperative) (mmHg)	165 ± 93.5	141 ± 65.4†	0.332
Partial pressure of CO_2 (preoperative) (mmHg)	41.4 ± 3.8	41.1 ± 4.8†	0.408
Partial pressure of CO_2 (postoperative) (mmHg)	41.2 ± 5.0	42.9 ± 4.5†	0.088
Metabolic status and body temperature			
pH (preoperative)	7.39 ± 0.06	7.40 ± 0.05	0.695
pH (postoperative)	7.37 ± 0.06	7.39 ± 0.05	0.088
Base excess (preoperative) (mEq/L)	0.1 ± 3.1†	0.2 ± 2.5	0.857
Base excess (postoperative) (mEq/l)	-1.6 ± 2.8†	0.6 ± 2.0	< 0.001*
Lactate concentration (preoperative) (mmol/L)	1.2 ± 1.2†	0.8 ± 0.4†	0.715
Lactate concentration (postoperative) (mmol/L)	2.9 ± 1.5†	2.3 ± 1.1†	0.030*
Body temperature (preoperative) (degrees Celsius)	36.3 ± 0.6†	36.4 ± 0.6†	0.686
Body temperature (postoperative) (degrees Celsius)	35.9 ± 0.8†	35.9 ± 0.6†	0.910
Hemodynamic data			
Mean arterial pressure (preoperative) (mmHg)	77.4 ± 16.0†	74.3 ± 12.0†	0.296
Mean arterial pressure (postoperative) (mmHg)	65.3 ± 7.86†	70.7 ± 9.73†	0.012*
Central venous pressure (preoperative) (mmHg)	9.80 ± 3.91†	8.79 ± 4.07†	0.276
Central venous pressure (postoperative) (mmHg)	11.8 ± 3.43†	10.6 ± 3.63†	0.173
Stroke volume (preoperative) (mL)	47.9 ± 14.3	50.4 ± 16.5	0.590
Stroke volume (postoperative) (mL)	45.7 ± 15.7	49.0 ± 16.9	0.511
Continuous cardiac output (preoperative) (L/min)	3.20 ± 0.76	3.54 ± 1.02	0.350
Continuous cardiac output (postoperative) (L/min)	3.84 ± 1.07	3.95 ± 1.27	0.995
CO_2 and O_2 derived parameters			
SvO_2 (preoperative) (%)	70.5 ± 9.55	75.9 ± 5.69†	0.512
SvO_2 (postoperative) (%)	70.7 ± 10.7	73.4 ± 7.68†	0.157
$ScvO_2$ (preoperative) (%)	76.5 ± 8.97	78.3 ± 6.94†	0.294
$ScvO_2$ (postoperative) (%)	74.1 ± 10.1	75.0 ± 7.62†	0.628
Pv-aCO_2 (preoperative) (mmHg)	5.76 ± 3.25	5.19 ± 2.23†	0.571
Pv-aCO_2 (postoperative) (mmHg)	8.30 ± 3.85	4.12 ± 2.07†	< 0.001*
Pcv-aCO_2 (preoperative) (mmHg)	7.26 ± 3.12	6.35 ± 3.10†	0.374
Pcv-aCO_2 (postoperative) (mmHg)	9.01 ± 4.15	5.95 ± 2.38†	< 0.001*
Ca-vO_2 (preoperative) (mL/dL)	4.06 ± 1.05	3.89 ± 0.93	0.365
Ca-vO_2 (postoperative) (mL/dL)	4.01 ± 1.33	3.79 ± 0.97	0.376
Ca-cvO_2 (preoperative) (mL/dL)	3.84 ± 1.18	3.63 ± 0.99	0.372
Ca-cvO_2 (postoperative) (mL/dL)	3.69 ± 1.29	3.63 ± 1.17	0.786

Table 7 (continued)

Variables	With MOMM (n = 25)	Without MOMM (n = 85)	p value
$Ca\text{-}vO_2 \times CCO$ (preoperative) (mL/min)	124 ± 39.0	136 ± 42.9	0.715
$Ca\text{-}vO_2 \times CCO$ (postoperative) (mL/min)	142 ± 50.7	149 ± 41.3	0.733
$Ca\text{-}cvO_2 \times CCO$ (preoperative) (mL/min)	115 ± 33.4	129 ± 43.6†	0.347
$Ca\text{-}cvO_2 \times CCO$ (postoperative) (mL/min)	129 ± 46.3	141 ± 43.0†	0.445
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (preoperative) (mmHg dL/mL)	1.61 ± 1.18†	1.42 ± 0.87†	0.547
$Pv\text{-}aCO_2/Ca\text{-}vO_2$ (postoperative) (mmHg dL/mL)	2.45 ± 1.89†	1.09 ± 0.52†	< 0.001*
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (preoperative) (mmHg dL/mL)	2.22 ± 1.65†	1.86 ± 0.98	0.895
$Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ (postoperative) (mmHg dL/mL)	2.82 ± 1.83†	1.73 ± 0.80	0.004*

Data are expressed as mean ± SD

MOMM major organ morbidity and mortality, *CPB* cardiopulmonary bypass, SvO_2 mixed venous oxygen saturation, $ScvO_2$ central venous oxygen saturation, $Pv\text{-}aCO_2$ mixed venous-to-arterial carbon dioxide gradient, $Pcv\text{-}aCO_2$ central venous-to-arterial carbon dioxide gradient, $Ca\text{-}vO_2$ arterial–mixed venous O_2 content difference, $Ca\text{-}cvO_2$ arterial–central venous O_2 content difference, *CCO* continuous cardiac output, $Pv\text{-}aCO_2/Ca\text{-}vO_2$ mixed venous–arterial carbon dioxide gradient to arterial–mixed venous O_2 content difference ratio, $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ central venous–arterial carbon dioxide gradient to arterial–central venous O_2 content difference ratio

*$p < 0.05$ statistically significant (between 2 groups), $^{\dagger}p < 0.05$ statistically significant (preoperative vs. postoperative)

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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