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Care of The Critically Ill

Increased admission central venous-arterial CO_2 difference predicts ICU-mortality in adult cardiac surgery patients

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ABSTRACT

Background: Invasive procedures such as cardiac surgery are associated with perioperative dysfunction of macrocirculation and/or microcirculation and organ failures. Maintenance or resuscitation of an adequate macrocirculation and/or microcirculation is thus crucial in patients after cardiac surgery. We investigated the prognostic power of early central venous-arterial carbon dioxide pressure difference (delta-pCO2) after cardiac surgery.
Methods: Retrospective analysis of data from 1,019 cardiac surgery patients treated in the ICU of a tertiary medical care academic center. Clinical outcomes and laboratory measures including metabolic indices and calculated delta-pCO_2 were assessed. Receiver operating characteristic (ROC) curves were generated and sensitivity / specificity analysis was performed. Univariate and multivariate regression models were analyzed.
Results: The area under the ROC curve for delta-pCO_2 to predict ICU mortality was 0.72 (sensitivity 65% / specificity 76%) with an optimal delta-pCO_2 cut-off value of 8.6 mmHg. In multivariate regression, delta-pCO_2 was associated with increased ICU mortality (HR 3.72, 95%-CI 1.3–10.66, $p = 0.02$). After adjustment for typical confounders, delta-pCO_2 remained as independent predictor of ICU mortality after cardiac surgery.
Conclusions: In a retrospective data analysis in a large sample of adult post cardiac surgery patients treated in the ICU, we observed that admission central venous-arterial delta-pCO_2 independently predicts ICU mortality. Delta-pCO_2 might thus contribute risk stratification in ICU patients after cardiac surgery.

Introduction

Maintenance of adequate tissue oxygenation is considered key in the care of critically ill patients. Optimization of hemodynamics and improvement of both metabolic status and tissue oxygen supply are primarily addressed via "goal-directed" therapies.[1,2] After cardiac surgery under hypothermia, impaired tissue oxygenation may occur for a number of reasons. First, the cardiopulmonary bypass may induce a systemic inflammatory response, leading to altered microcirculation and/or increased cellular oxygen demand.[3–5] Further, changes in vasotone may induce a discrepancy between blood flow and (metabolic) demand.[6] Hence, an adequate macrocirculation status (i.e., both cardiac output and perfusion pressures) may exist despite impaired microcirculation.

Cardiac surgery patients undergoing operations with cardiopulmonary bypass typically have relevant macro- and microcirculation changes[3–5,7] which may alter perioperative carbon dioxide (CO_2) metabolism. Delta-pCO_2 (i.e., central venous CO_2 partial pressure minus arterial CO_2 partial pressure) reflects the difference between CO_2 production and clearance. Under physiological conditions, delta-pCO_2 was shown not to exceed 6 mmHg.[8] Based on Fick's equation, delta-pCO_2 is proportional to CO_2 production and inversely related to cardiac output as a part of macrocirculation.[9] Delta-pCO_2 has been found to increase when cardiac output decreases.[10,11] Therefore, when cardiac output is adjusted to oxygen consumption (VO_2), delta-

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pCO_2 may not increase due to the concomitance increased CO_2-clearance. In terms of reduced cardiac output, delta-pCO_2 should increase due to the CO_2 stagnation phenomenon.[12] Even when microcirculation is preserved, increased delta-pCO_2 to be an effect of reduced cardiac output.[12]

Microcirculatory investigations may thus reveal the relationship between pCO_2 and capillary perfusion deficits,[13] and delta-pCO_2 has been proposed a marker of microvascular blood flow.[14] Decreased local blood low flow states in an experimental setting (ischemic hypoxia) has been shown to be related to increased regional delta-pCO_2 due to the CO_2 stagnation phenomenon,[15] even when no additional CO_2-production occurred due to hypoxia.[12] Hence, increased delta-pCO_2 may reflect both reduced cardiac output (macrocirculation) and coexisting altered tissue perfusion (microcirculation).

In fact, metabolic and/or oxygenation indices including base excess (BE) ,[16] central venous saturation ($ScvO_2$) ,[3,17] lactate-levels,[18–21] or serum pH[22] may only partially reflect tissue oxygenation and perfusion in acute cardiac patients. In a previous study increased delta-pCO_2 (i.e. about 6–8 mmHg) was identified as a predictor for mortality in patients with sepsis.[23] Only limited data from small cohorts ($n = 60–393$) with heterogeneous outcome prediction results are available for delta-pCO_2 in cardiac surgery patients.[24–27] Overall, early recognition of patients at increased risk may be regarded as pivotal for risk stratification and development of novel treatment approaches. This highlights the need for additional prognostic markers. Moreover, few parameters indicate (or are associated with) mortality in cardiac surgery patients. In light of the paucity of available data on delta-pCO_2 in respective patients, we aimed to investigate its potential prognostic role as an additional parameter to predict outcome in a large mixed population of cardiac surgery patients in the postoperative ICU.

Material and methods

Design and setting

This investigation is a part of the Cardiac surgery Database Project that studied metabolic aspects in cardiac surgery patients.[28] We retrospectively analyzed data from 1292 cardiac surgery patients hospitalized in a 14-bed ICU in the Department of Intensive Care Medicine of a tertiary care academic center. Data from a predefined period (February 2009 to March 2010) were analyzed.

Inclusion/ exclusion criteria

Patients aged <18 were excluded from the analysis. Patients receiving implanted cardiac assist devices (extracorporeal membrane oxygenation, ventricular assist device), patients who received off-pump surgery and patients undergoing heart/lung transplantation were excluded from this investigation. Data from patients undergoing routine and emergency cardiac operations were included.

Ethical considerations

Ethical approval and informed consent for this retrospective observational data analysis were waived based on the study's used of anonymized data (Research Ethics Committee of the Hamburg Chamber of Physicians). The study adheres to the Declaration of Helsinki.

Data assessment

Demographic data, risk assessment (EUROscore, European System for Cardiac Operative Risk Evaluation), preoperative existing co-morbidities (chronic obstructive pulmonary disease, COPD; renal impairment, defined as serum creatinine >200 μmol/L; severe reduced left ventricular function (LVEF, defined as ejection fraction <35%), and perioperative and intraoperative data were recorded. Hemodynamic support (but not detailed hemodynamic measurement) at admission with inotropic/vasopressor agents or phosphodiesterase (PDE) inhibitors, blood gas analyses (BGA) on admission to the ICU, duration of mechanical ventilation, lengths of ICU stay and ICU mortality were available for analysis.

Patient treatment

Anesthesia, surgery, cardiopulmonary bypass, and postoperative care on the ICU were performed according to the hospital's standard operating procedures. There were no changes to the routine standards of care during the assessment period.

Routine data on oxygenation and metabolic parameters derived from blood samples drawn from central venous catheters. Data from arterial temperature-corrected BGAs derived from routinely placed arterial catheters. Arterial and central venous blood samples were drawn immediately after postoperative admission to the ICU. Point-of-care blood gas analysis was performed on the ICU (Radiometer Copenhagen, ABL 700 Series, Willich, Germany). Central venous-arterial carbon dioxide content difference was calculated based on available data on admission blood gas analyses ($pcvCO_2$ $paCO_2$ = delta-pCO_2).

Typical extubation criteria were stable hemodynamics and gas exchange under moderate pressure support/ PEEP ($paO_2 > 60$ mmHg, $FiO_2 < 0.4$), ability to obey commands, and presumed ability to protect the airway. Typical ICU discharge criteria were neurological adequateness (i.e. patients without delirium or agitation), hemodynamically stable condition without vasopressor support and balanced metabolic status, and stable pulmonary conditions with only low oxygen-supply.

Statistical analysis

Statistical analysis was performed using MedCalc 17.4 (MedCalc Software, Ostend, Belgium). The Kolmogorov-Smirnov test was used to check for normal distribution. Continuous variables are presented as median/ interquartile range (IQR). Categorical variables are given as absolute numbers and proportions, if appropriate. Univariate regression followed by multivariate regression was performed. Receivers operating characteristic (ROC) curves with area under the ROC curve (AUROC) were generated for delta-pCO_2, BE, and pH including between-ROC curve comparison to evaluate the diagnostic ability of these biomarkers. Youden's index was used to define the maximum potential efficiency of the biomarker delta-pCO_2. The calculated optimal cut-off value optimizes delta-pCO_2 differentiating ability when equivalent weight is given to sensitivity (Se) and specificity (Sp) ($J = \max_c$ [Se (c) + Sp (c) – 1]; c: cut off-point). Comparison of survivors and non-survivors based on highest sensitivity/ specificity cut-offs for delta-pCO2 was performed using the Mann–Whitney U test, Chi-squared-test, or Fisher's exact test. A two-tailed $p < 0.05$ was considered statistical significant.

Results

Patient demographics and delta pCO_2

Out of 1292 data sets, 1019 were eligible for study inclusion after careful assessment of the exclusion criteria. The CONSORT flowchart is given in Fig. 1. Demographics and perioperative data are displayed in Table 1. In these patients coronary artery bypass grafting (CABG) was performed in 36.7% ($n = 374$), valve-operations in 31.11% ($n = 317$), combined CABG and valve-operations in 18.25% ($n = 186$), major aortic surgery in 9.72% ($n = 99$) and in 4.22% ($n = 43$) other cardiac surgery procedures.

During the ICU-stay, 1.96% ($n = 20/1019$) of patients died. ICU non-survivors had a higher EuroSCORE (European System for

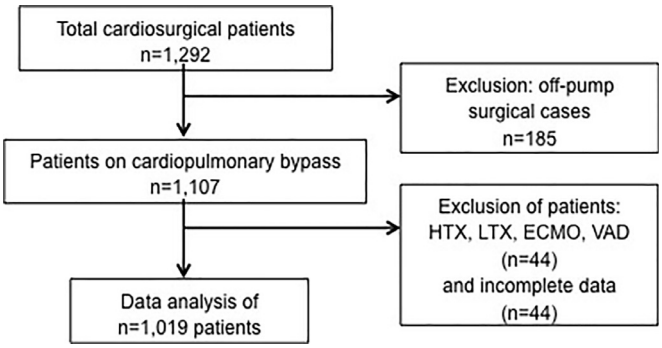

Fig. 1. Flow chart. HTX: heart transplantation, LTX: lung transplantation, ECMO: extracorporeal membrane oxygenation, VAD: ventricular assist device.

Table 1
Patient demographics and perioperative data.

	All patients (n = 1019)	ICU survivors (n = 999)	ICU non-survivors (n = 20)	Between group p
Gender (female,%)	333 (33)	327 (33)	6 (30)	(1.0)[a]
Age (year)	69.7 (61.4–75.4)	69.7 (61.3–75.4)	71.5 (66.5–74.4)	0.67
Weight (kg)	80 (69–90)	80 (69–90)	79 (72–90)	(1.0)
Height (cm)	172 (166–178)	172 (166–178)	173 (169–178.5)	0.75
EuroSCORE, additive	4 (2–6)	4 (2–6)	7 (3.5–9)	0.001
Emergency operation (%)	67 (6.6)	63 (6.31)	4 (20.0)	0.04[a]
Cardiopulmonary bypass time (min)	128 (102–166)	127.5 (101–165)	225 (143–258)	<0.001
Aortic cross clamp time (min)	83 (63–108)	82 (62.5–107)	121 (90.8–145.8)	<0.001
Epinephrine at admission (μ/kg/min)	0 (0–0.01)	0 (0 – 0.01)	0.06 (0–0.13)	<0.0001
Norepinephrine at admission (μ/kg/min)	0.01 (0–0.04)	0.01 (0–0.03)	0.12 (0.01–0.31)	<0.0001
PDE-support at admission (%)	58 (5.7)	50 (5.01)	8 (40.0)	<0.0001[a]
Mech. ventilation (hours)	8.7 (5.8–13.0)	8.7 (5.8–12.7)	44.8 (15.4–160.3)	<0.001
Length of stay on ICU (days)	2 (2–3)	2 (2–3)	5 (2–9.5)	<0.001
Pre-existing clinical conditions				
COPD (%)	83 (8.1)	82 (8.2)	1 (5.0)	(1.0)[a]
Renal impairment (%)	62 (6.1)	61 (6.1)	1 (5.0)	(1.0)[a]
Pulmonary hypertension (%)	27 (2.6)	25 (2.5)	2 (10.0)	(0.1)[a]
Severely reduced LVEF (%)	74 (7.3)	68 (6.8)	6 (30.0)	0.002[a]
Re-operation (%)	37 (3.6)	33 (3.3)	4 (20.0)	0.005[a]
Parameters at ICU admission				
Delta-pCO_2 (mmHg)	7.0 (5.6–8.6)	7.0 (5.6–8.6)	9.55 (7.1–11.4)	0.001
Delta-pCO_2 > 6 mmHg (%)	691 (67.8)	674 (67.5)	17 (85)	0.15[a]
Delta-pCO_2 > 8.6 mmHg (%)	254 (24.9)	241 (24.12)	13 (65)	0.0002[a]
$paCO_2$ (mmHg)	39.8 (35.9–44.3)	39.8 (35.9–44.3)	40.2 (36.8–47.3)	0.37
$pcvCO_2$ (mmHg)	47 (43.5–51.1)	46.9 (43.5–51.1)	50.2 (44.9–56.9)	0.03
Arterial pH (mmHg)	7.36 (7.31–7.4)	7.36 (7.32–7.4)	7.32 (7.22–7.36)	0.002
Arterial Base excess	−2.5 (−4 - −1.3)	−2.5 (−4 - −1.2)	−5.6 (−8.1 - −2.2)	0.002
Hemoglobin (g/dl)	10 (9.3–10.7)	10 (9.3–10.7)	10.2 (9.15–10.6)	0.92
Temperature (C°)	36.2 (35.9–36.6)	36.2 (35.9–36.6)	35.7 (35.6–36.6)	0.041
ICU mortality rate (%)	1.96 (20)	–	–	–

Data are presented as median and interquartile range, or absolute frequencies. Mann–Whitney-U test, Chi^2 test.
ICU: intensive care unit, BMI: body mass index, EuroSCORE: European System for Cardiac Operative Risk Evaluation, PDE: phosphodiesterase-3-inhibitor, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction.
[a] Fisher's exact test.

Cardiac Operative Risk Evaluation), longer CPB- and aortic cross-clamp times (AOX-time), as well as longer duration of mechanical ventilation (Table 1). No statistically significant differences were noted with regard to presence of pre-existing co-morbidities (e.g. COPD, chronic kidney disease or pulmonary hypertension) (Table 1). Non-survivors received emergency operations more frequently and more often had reduced left ventricular ejection fractions (LVEF). Further, non-survivors required higher and more frequent doses of epinephrine, norepinephrine, and PDE-inhibitors (Table 1). Moreover, data from blood gas analyses showed both higher $pcvCO_2$ and delta-pCO_2, lower base excess (BE), reduced serum pH levels, and reduced core body temperatures in non-surviving patients (Table 1). A significant difference was evident in the proportion of survivors/ non-survivors with delta-pCO_2 > 8.6 mmHg (Table 1).

A comparison of data from patients with delta-pCO_2 ≤ 8.6 mmHg and delta-pCO_2 >8.6 mmHg appears in Table 2. Patients with high delta-pCO_2 were more likely to be of female gender and had lower body weight and height (Table 2). No differences were found with regard to body mass index (BMI), disease severity as assessed by the EUROscore,[29] CPB-time and AOX-time (Table 2). Patients with high delta-pCO_2 (>8.6 mmHg) received longer mechanical ventilation and had longer ICU stay, more severely reduced LVEF, lower arterial pCO_2, increased BE, and higher pH when compared to patients with delta-pCO_2 ≤ 8.6 mmHg (Table 2). Overall ICU mortality was 5.12% in patients with high (>8.6 mmHg) delta-pCO_2 vs. 0.92% in patients with high (>8.6 mmHg) delta-pCO_2 ($p < 0.0001$, Table 2).

Sensitivity and specificity analysis

Pairwise comparison of ROC curves revealed no statistical difference between respective ROC curves (delta-pCO_2 vs. BE: between ROC $p = 0.93$; delta-pCO_2 vs. pH: between ROC $p = 0.96$; BE vs. pH: between ROC $p = 0.94$). Optimal sensitivity and specificity for delta-

Table 2
Patient demographics and perioperative data related to delta-pCO_2.

	Delta-$pCO_2 \leq 8.6$ mmHg ($n = 765$)	Delta-$pCO_2 > 8.6$ mmHg ($n = 254$)	Between group *P* value
Gender (female,%)	235 (30.72)	98 (38.58)	0.02
Age (year)	69.5 (60.9–75.2)	70.6 (62.6–75.8)	0.11
Weight (kg)	80 (70–90)	77 (67–86)	0.03
Height (cm)	173 (167–179)	171 (164–177)	0.01
EuroSCORE, additive	4 (2–6)	4 (3–6)	0.051
Emergency operation (%)	45 (5.9)	22 (8.7)	0.12
Cardiopulmonary bypass time (min)	128 (100–163)	127 (105–179)	0.11
Aortic cross clamp time (min)	82 (63–107)	84.5 (63–110)	0.31
Epinephrine at admission (μ/kg/min)	0 (0–0.01)	0 (0–0.01)	0.73
Norepinephrine at admission (μ/kg/min)	0.01 (0–0.03)	0.01 (0–0.04)	0.18
PDE-support at admission (%)	43 (5.6)	15 (5.91)	0.87
Mech. ventilation (hours)	8.5 (5.7–12.3)	9.8 (6.9–15.5)	<0.001
Length of stay on ICU (days)	2 (2–3)	2 (2–4)	0.02
Pre-existing clinical conditions			
COPD (%)	63 (8.24)	20 (7.87)	0.86
Renal impairment (%)	53 (6.93)	9 (3.54)	0.05
Pulmonary hypertension (%)	17 (2.22)	10 (3.94)	0.14
Severely reduced LVEF (%)	48 (6.28)	26 (10.24)	0.04
Re-operation (%)	24 (3.14)	13 (5.11)	0.14
Parameters at ICU admission			
Delta-pCO_2 (mmHg)	6.4 (5.1–7.4)	10 (9.2–11.2)	<0.0001
$paCO_2$ (mmHg)	40.9 (37.1–45.1)	37 (32.5–40.7)	<0.0001
$pcvCO_2$ (mmHg)	46.9 (43.6–50.9)	47.2 (43.2–51.7)	0.49
Arterial pH (mmHg)	7.35 (7.31–7.39)	7.37 (7.33–7.42)	<0.0001
Arterial base excess	−2.4 (−3.9– −1.2)	−2.8 (−4.5- −1.3)	0.03
Hemoglobin (g/dl)	10 (9.3–10.7)	10.1 (9.2–10.6)	0.55
Temperature (C°)	36.2 (35.9–36.6)	36.2 (35.9–36.6)	0.03
ICU mortality rate (%)	7 (0.92)	13 (5.12)	<0.0001

Data presented as median and interquartile range, or absolute frequencies. Mann–Whitney-*U* test or Chi^2 test. ICU: intensive care unit, BMI: body mass index, EuroSCORE: European System for Cardiac Operative Risk Evaluation, PDE: phosphodiesterase-3-inhibitor, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction.

pCO_2 was 65% and 75.9%, respectively (Youden's index 0.41). A delta-pCO_2 cut-off value of 8.6 mmHg thus best differentiated between survivors and non-survivors in the cohort under investigation.

Correlation analysis of delta-pCO_2

Delta-pCO_2 was positively correlated with pH ($r = 0.16$, $p < 0.0001$, 95% CI 0.1 to 0.22) at admission, EuroSCORE ($r = 0.06$, $p = 0.04$, 95%-CI 0 to 0.13) and CPB-time ($r = 0.07$, $p = 0.02$, 95%-CI 0.01 to 0.13). A negative correlation was observed for BE ($r = -0.06$, $p = 0.047$, 95%-CI −0.12 to 0) at admission. No correlation was observed between delta-pCO2 and norepinephrine or epinephrine-dose, hemoglobin levels and admission core body temperature (all $p > 0.12$).

Univariate and multivariate regression

In univariate regression, the EuroSCORE, CPB-time, PDE-support at ICU admission, pre-existing severely reduced LVEF, previous cardiac surgery, delta-pCO_2, arterial pH, and BE were associated with increased ICU-mortality (Table 3). In a first model with three degrees of freedom, admission delta-pCO_2 (continuous variable), was identified an independent predictor of ICU-mortality after adjustment for EuroSCORE and CPB-time (hazard ratio 1.17, 95%-CI 1.01–1.36, $p = 0.04$, Wald 4.08; overall fitness of model Chi^2 13.11, $p = 0.004$). Moreover, multivariate regression models for ICU mortality identified delta-pCO_2 >8.6 mmHg as independent predictor for ICU-mortality after adjustment for disease severity (EuroSCORE), CPB-time, and BE (Table 3, overall model fitness Chi^2 19.97, $p = 0.0005$).

Mortality rates in the ICU were 1.18% ($n = 3$) in the 1st (lower) delta-pCO2 quartile, 0.78% in the 2nd quartile ($n = 2$), 0.78% in the 3rd quartile ($n = 2$), and 5.1% in the 4th (upper) quartile ($n = 13$). Median and IQRs for delta-pCO_2 and respective hazard ratio are given in table 4.

Discussion

In this study we investigated metabolic and oxygenation indices including delta-pCO_2 with regard to predictive power in adult post cardiac surgery patients. Following univariate and multivariate regression models, we observed that delta-$pCO_2 > 8.6$ mmHg independently predicts ICU-mortality in post-cardiac surgery patients.

Cardiac surgery patients undergoing CPB operations typically show signs of macro- and micro-hemodynamic changes.[3–5,7] Conditions leading to circulatory changes may induce altered CO_2- metabolism in the early postoperative phase.[9,30] Previous microcirculatory investigations have revealed a relationship between pCO_2 and capillary perfusion deficits,[13] and delta-pCO_2 was thus proposed a marker of microvascular blood flow[14] and associated with conditions leading to tissue hypoxia.[31,32] Additionally, increased delta-pCO_2 may reflect low cardiac output.[9] Hence, elevated delta-pCO_2 on ICU admission may reflect both coexisting mechanisms - low cardiac output (independent from microcirculation) and/or impaired microcirculation (independent of cardiac output).

Previously available data on 165 cardiac surgery patients from Morel et al. appear to show that delta-pCO_2 <6 mmHg six hours after ICU admission is associated with increased mortality.[33] However, admission data were not analyzed in that study. Our analysis shows a reduction in the risk of mortality when comparing the lowest quartile of delta-pCO_2 with the second or third delta-pCO_2 quartile (Table 4). Similarly, a reduction in the risk of mortality was also observed when switching from the upper quartile to third or second quartiles. Thus, it is tempting to speculate that delta-pCO_2 influences mortality in a U-shaped fashion, i.e. with the highest mortality in highest and lowest delta-pCO_2 ranges, which appears comparable to other biomarkers and physiological variables (e.g. serum bicarbonate). As a result, admission delta $pCO_2 > 8.6$ mmHg was therefore deliberately included to the MV model (Table 3).

Table 3
Univariate and multivariate regression models.

	Univariate model for ICU mortality			Multivariate model for ICU mortality		
	Hazard ratio (95% CI)	*P* value	Wald	Hazard ratio (95% CI)	*P* value	Wald
Gender (female)	0.84 (0.32–2.22)	0.73	0.1	–	-	–
Age (per 1 year increase)	0.98 (0.95–1.02)	0.39	0.4	–	-	–
Weight (per 1 kg increase)	1.0 (0.97–1.03)	0.98	0	–	–	–
Height (per 1 cm increase)	1.01 (0.96–1.06)	0.77	0.1	–	–	–
EuroSCORE, additive (per 1 step increase)	1.18 (1.04–1.34)	0.01	6.4	1.12 (0.95–1.28)	0.2	1.7
Emergency operation (y/n)	1.59 (0.46–5.59)	0.46	0.5	–	–	–
Cardiopulmonary bypass time (per 1 min increase)	1.01 (1.0–1.01)	0.006	7.5	1.0 (1.0–1.01)	0.12	2.47
Aortic cross clamp time (per 1 min increase)	1.01 (1.0–1.01)	0.2	1.6	–	–	–
Mechanical vent. (per 1 h increase)	1.0 (1.0–1.0)	0.81	0.1	–	–	–
PDE-support at admission (y/n)	3.04 (1.11–8.35)	0.03	4.7	–	–	–
Pre-existing clinical conditions						
COPD (y/n)	0.52 (0.07–3.92)	0.53	0.4	–	–	–
Renal impairment (y/n)	0.49 (0.07–3.69)	0.49	0.5	–	–	–
Pulmonary hypertension (y/n)	3.11 (0.71–13.71)	0.13	2.3	–	–	–
Severely reduced LVEF (y/n)	3.93 (1.45–10.64)	0.007	7.2	–	-	–
Re-operation (y/n)	4.23 (1.36–13.12)	0.01	6.2	–	–	–
Parameters at admission on ICU				–	–	–
Delta-pCO_2 (per 1 mmHg increase)	1.25 (1.09–1.44)	0.001	10.6	–	–	–
Delta-pCO_2 >6 mmHg	2.53 (0.74–8.71)	0.14	2.2	–	–	–
Delta-pCO_2 >8.6 mmHg	5.73 (2.15–15.29)	<0.0001	12.1	3.72 (1.3–10.66)	0.02	5.94
$paCO_2$ (per 1 mmHg increase)	1.02 (0.95–1.09)	0.59	0.3	–	–	–
$pcvCO_2$ (per 1 mmHg increase)	1.06 (1.0–1.13)	0.06	3.5	–	–	–
Arterial pH (per 1 unit increase)	0.002 (0–5.01)	0.03	4.9	-	–	–
Arterial base excess (per 1 unit increase)	0.85 (0.74–0.96)	0.01	6.6	0.87 (0.75–1.0)	0.06	3.62
Hemoglobin (per 1 g/dl increase)	0.97 (0.68–1.39)	0.86	0.03	–	–	–
Temperature (per 1 C° increase)	0.64 (0.41–1.0)	0.05	3.8	–	–	–

Hazard ratios with 95% confidence intervals are given for univariate and multivariate regression models. "-" denotes not included in model.

Table 4
Delta-pCO_2 after grouping for quartiles.

		1st (lower) quartile	2nd quartile	3rd quartile	4th (upper) quartile
	Median (IQR)	Hazard ratios with 95% confidence intervals			
1st (lower) quartile	4.7 (4.1–5.1)	–	0.71 (0.2–2.61)	0.58 (0.17–1.99)	3.8 (1.11–13.04)
2nd quartile	6.4 (6–6.7)	1.4 (0.38–5.11)	–	0.81 (0.23–2.86)	5.32 (1.51–18.68)
3rd quartile	7.8 (7.4–8.2)	1.72 (0.5–5.89)	1.23 (0.35–4.31)	–	6.53 (1.99–21.49)

Data for delta-pCO_2 are given in median and interquartile range (IQR).

Previous investigations (n = 393) provided a cut-off of 6 mmHg for delta-pCO_2 at ICU admission after cardiac surgery and did not observe an association with postoperative complications or mortality.[26] However, direct comparison of data may be difficult due to both a limited sample size and missing detailed information on the distribution of delta-pCO_2 levels among survivors/ non-survivors. However, a cut-off value of 6 mmHg delta-pCO_2 may misjudge distinct pathophysiological conditions in patients after extracorporeal circulation when compared, for example, to sepsis patients or patients without CPB-surgery.[7,30,34,35] In addition, additional delta-pCO_2 data deriving from cohorts with limited sample sizes (i.e. 10 to 140 patients) may not allow for investigation of outcome indices.[7,35,36] Nevertheless, few previous data observed in a subgroup of cardiac surgery patients with $ScvO_2$ > 70% (n = 25) and delta-pCO_2 > 8 mmHg (n = 4) show associations with longer need for mechanical ventilation and increased length of ICU-stay.[24]

Comparison of ROC curves depicting on ICU mortality showed no difference with regard to AUCs of delta-pCO_2, pH, or BE. This seems interesting as baseline bicarbonate levels were recently shown to predict mortality in heart failure/ cardiogenic shock[37,38] and admission base deficit in mixed ICU populations and in cardiac surgery patients may serve as a general risk indicator.[28,39]

Our analysis has limitations that deserve discussion. First, due to the retrospective study design and limited availability of data, details were not available for cardiac output, ventilator settings, and/or calorimetric data, course of other prognostically important indices and/or in-hospital- or 30-days mortality. The retrospective study design may have introduced bias, and we are, by definition, unable to come to any conclusions on underlying (patho-) mechanisms. In this light, we would like to emphasize the need for larger, prospective investigations that take ventilators settings and measured cardiac output into account.

The current controversial discussion of delta-pCO_2 in critically ill patients[14,25,26,40] triggered this retrospective analysis and this is the reason why data collected in the years 2009–2010 were re-analyzed. Importantly, treatment standards remained unchanged during the study interval and appear comparable to current treatment standards. The present investigation supports the notion that delta-pCO2 may be useful in the postoperative phase of medical care. Second, the sample size was limited with a corresponding limited number of non-surviving patients at ICU discharge, limiting our statistical model. Data on mid-term outcome and course of disease severity was also not available. Moreover, the EuroSCORE is typically used for risk stratification in this specific cohort of patients[41] and was deliberately included to the multivariate model to adjust for disease severity. This was considered inevitable in the specific context discussed. Inclusion of disease severity scores might have introduced some degree of co-linearity. Importantly, when admission delta-pCO_2 > 8.6 mmHg was replaced by admission delta-pCO_2 (continuous variable), it still remained a predictor of ICU-mortality in multivariate regression with three degrees of freedom. However, the limited number of event-rates (non-surviving patients n = 20) prevented adjustment for

additional confounders. Further, correlation of delta-pCO_2 and CPB-time may be explained by impaired perfusion and metabolic disorders by CPB,[35] which could have been caused e.g. by compromised splanchnic blood flow[7] or microcirculatory alterations and heterogeneity.[4,42,43] However, our results confirm a correlation of delta-pCO_2 and duration of CPB-time. Inevitable in this specific context of the association of delta-pCO_2 > 8.6 mmHg and duration of CPB-time, we believe including CPB-time in the multivariate model may have introduced a minor bias only. Third, our findings are limited by the fact that only data at ICU admission and ICU outcome data were available, which limits comparability to previous investigations. Thus, our study focuses on short term (i.e. ICU-mortality) but not on midterm, or long-term outcomes. Fourth, detailed intraoperative (and postoperative) hemodynamic data were not available. Thus, the specific origin of macrocirculatory or microcirculatory disorders cannot be identified, which prevents us from drawing of conclusions on potential risk factors or causal mechanisms influencing postoperative delta-pCO_2. Due to complex, potentially coexisting circulatory disorders, interpretation of delta-pCO_2 should be made in the clinical context and/or in light of other hemodynamic and/or metabolic variables only. Fifth, hypothermia during extracorporeal circulation and the slope of postoperative rewarming may have affected CO_2-production and thus partial CO_2-pressure and CO_2-content.[44] However, on ICU admission, lower $paCO_2$ levels were noted in patients with delta-pCO_2 > 8.6 mmHg. This may be due to the fact that a decline in $pcvCO_2$ may lag behind a decrease in $paCO_2$ instead of the CO_2 stagnation phenomenon, which in turn may lead to increased delta-pCO_2.[45] Moreover, acute hyperventilation might increase delta-pCO_2 but, as mentioned before, detailed data on ventilator settings were unavailable.[40]

Conclusions

In a large cohort of adult post cardiac surgery ICU patients, we observed that increased central venous-arterial delta-pCO_2 at ICU admission predicted ICU mortality after adjustment for typical confounders. Delta-pCO_2 may appear as an additional parameter to help identify postoperative cardiac surgery patients at increased risk of mortality. Given the widespread availability of delta-pCO_2, we support including delta-pCO_2 to the indices used for follow-up and risk assessment in this specific ICU population and propose performing of larger prospective analyses in this regard.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.05.015.

References

1. Carl M, Alms A, Braun J, et al. S3 guidelines for intensive care in cardiac surgery patients: hemodynamic monitoring and cardiocirculary system. *Ger Med Sci*. 2010;8. Doc12.
2. Kapoor PM, Magoon R, Rawat R, Mehta Y. Perioperative utility of goal-directed therapy in high-risk cardiac patients undergoing coronary artery bypass grafting: A clinical outcome and biomarker-based study. *Ann Card Anaesth*. 2016;19 (4):638–682.
3. Zante B, Kubik M, Reichenspurner H. Combination of high ScvO2 and hyperlactatemia as sign of microcirculation disorder in patients after cardiac surgery. *Thorac Cardiovasc Surg*. 2012;60(S 01):P20. 18.01.2012.
4. Koning NJ, Simon LE, Asfar P, Baufreton C, Boer C. Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. *Am J Physiol Heart Circ Physiol*. 2014;307(7):H967–H975. Oct 01.
5. Spiess BD. Critical oxygen delivery: the crux of bypass with a special look at the microcirculation. *J Extra Corpor Technol*. 2011;43(1):P10–P16.
6. Ruokonen E, Takala J, Kari A. Regional blood flow and oxygen transport in patients with the low cardiac output syndrome after cardiac surgery. *Crit Care Med*. 1993;21(9):1304–1311.
7. Ruokonen E, Soini HO, Parviainen I, Kosonen P, Takala J. Venoarterial CO2 gradient after cardiac surgery: relation to systemic and regional perfusion and oxygen transport. *Shock*. 1997;8(5):335–340.
8. Steinberg JJ, Harken AH. The central venous catheter in the assay of acid base status. *Surg Gynecol Obstet*. 1981;152(2):221–222.
9. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med*. 2005;31(6):818–822.
10. Zhang H, Vincent JL. Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. *Am Rev Respir Dis*. 1993;148(4 Pt 1):867–871.
11. Van der Linden P, Rausin I, Deltell A, et al. Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. *Anesth Analg*. 1995;80(2):269–275.
12. Teboul JL, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. *Crit Care Med*. 1998;26(6):1007–1010.
13. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med*. 2006;32(4): 516–523.
14. Ospina-Tascon GA, Umana M, Bermudez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock. *Intensive Care Med*. 2016;42(2):211–221.
15. Vallet B, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol (1985)*. 2000;89(4):1317–1321. Oct.
16. Murray DM, Olhsson V, Fraser JI. Defining acidosis in postoperative cardiac patients using Stewart's method of strong ion difference. *Pediatr Crit Care Med*. 2004;5 (3):240–245.
17. Balzer F, Sander M, Simon M, et al. High central venous saturation after cardiac surgery is associated with increased organ failure and long-term mortality: an observational cross-sectional study. *Critical Care*. 2015;19(1):168. 2015.
18. Totaro RJ, Raper RF. Epinephrine-induced lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25(10):1693–1699. 1997.
19. Raper RF, Cameron G, Walker D, Bowey CJ. Type B lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25(1):46–51. 1997.
20. Landow L. Splanchnic lactate production in cardiac surgery patients. *Crit Care Med*. 1993;21(2 Suppl):S84–S91.
21. Cohen RD, Woods HF. Lactic acidosis revisited. *Diabetes*. 1983;32(2):181–191.
22. Frantz TL, Gaski GE, Terry C, Steenburg SD, Zarzaur BL, McKinley TO. The effect of pH versus base deficit on organ failure in trauma patients. *J Surg Res*. 2016;200 (1):260–265.
23. Ospina-Tascon GA, Bautista-Rincon DF, Umana M, et al. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. *Crit Care*. 2013;17(6):R294. Dec 13.
24. Habicher M, von Heymann C, Spies CD, Wernecke KD, Sander M. Central venous-arterial pCO2 difference identifies microcirculatory hypoperfusion in cardiac surgical patients with normal central venous oxygen saturation: a retrospective analysis. *J Cardiothorac Vasc Anesth*. 2015;29(3):646–655.
25. Morel J, Grand N, Axiotis G, et al. High veno-arterial carbon dioxide gradient is not predictive of worst outcome after an elective cardiac surgery: a retrospective cohort study. *J Clin Monit Comput*. 2016;30(6):783–789.
26. Guinot PG, Badoux L, Bernard E, Abou-Arab O, Lorne E, Dupont H. Central venous-to-arterial carbon dioxide partial pressure difference in patients undergoing cardiac surgery is not related to postoperative outcomes. *J Cardiothorac Vasc Anesth*. 2017;31(4):1190–1196. Feb 03.
27. Rhodes LA, Erwin WC, Borasino S, Cleveland DC, Alten JA. Central venous to arterial CO2 difference after cardiac surgery in infants and neonates. *Pediatr Crit Care Med*. 2017;18(3):228–233.
28. Zante B, Reichenspurner H, Kubik M, Kluge S, Schefold JC, Pfortmueller CA. Base excess is superior to lactate-levels in prediction of ICU mortality after cardiac surgery. *Plos One*. 2018;13:(10): e0205309.
29. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg*. 1999;15(6):816–822. discussion 822-813.
30. Vallee F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock. *Intensive Care Med*. 2008;34(12):2218–2225.
31. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med*. 1986;315(3):153–156. Jul 17.
32. Johnson BA, Weil MH. Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses. *Crit Care Med*. 1991;19 (11):1432–1438.
33. Morel J, Bouchet JB, Vola M, et al. Tissue near infra red spectroscopy change is not correlated with patients' outcome in elective cardiac surgery. *Acta Anaesthesiol Scand*. 2014;58(7):835–842.
34. Futier E, Robin E, Jabaudon M, et al. Central venous O(2) saturation and venous-to-arterial CO(2) difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care*. 2010;14(5):R193.
35. Takami Y, Masumoto H. Mixed venous-arterial CO2 tension gradient after cardiopulmonary bypass. *Asian Cardiovasc Thorac Ann*. 2005;13(3):255–260.
36. Ariza M, Gothard JW, Macnaughton P, Hooper J, Morgan CJ, Evans TW. Blood lactate and mixed venous-arterial PCO2 gradient as indices of poor peripheral

perfusion following cardiopulmonary bypass surgery. *Intensive Care Med*. 1991;17(6):320–324.
37. Wigger O, Bloechlinger S, Berger D, et al. Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *Eur Heart J Acute Cardiovasc Care*. 2016;7(1):45–52. Dec 01. 2048872616683526.
38. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol*. 2016;12(10):610–623.
39. Bezerra IS, Ribeiro E, Peixoto Junior AA, Meneses FA. [Base deficit at intensive care unit admission: an early mortality indicator]. *Rev Bras Ter Intensiva*. Dec 2007;19(4):434–436.
40. Mallat J, Mohammad U, Lemyze M, et al. Acute hyperventilation increases the central venous-to-arterial PCO2 difference in stable septic shock patients. *Ann Intensive Care*. 2017;7(1):31.
41. Tsaousi GG, Pitsis AA, Ioannidis GD, Pourzitaki CK, Yannacou-Peftoulidou MN, Vasilakos DG. Implementation of EuroSCORE II as an adjunct to APACHE II model and SOFA score, for refining the prognostic accuracy in cardiac surgical patients. *J Cardiovasc Surg (Torino)*. 2015;56(6):919–927.
42. Feng J, Liu Y, Chu LM, et al. Changes in microvascular reactivity after cardiopulmonary bypass in patients with poorly controlled versus controlled diabetes. *Circulation*. 2012;126(11 Suppl 1):S73–S80. Sep 11.
43. Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R. Effect of a maldistribution of microvascular blood flow on capillary O(2) extraction in sepsis. *Am J Physiol Heart Circ Physiol*. 2002;282(1):H156–H164.
44. Hanhela R, Mustonen A, Korhonen I, Salomaki T. The effects of two rewarming strategies on heat balance and metabolism after coronary artery bypass surgery with moderate hypothermia. *Acta Anaesthesiol Scand*. 1999;43(10):979–988.
45. McEvoy JD, Jones NL, Campbell EJ. Mixed venous and arterial Pco2. *Br Med J*. 1974;4(5946):687–690. Dec 21.