Original Article

The Use of the Ratio between the Veno-arterial Carbon Dioxide Difference and the Arterial-venous Oxygen Difference to Guide Resuscitation in Cardiac Surgery Patients with Hyperlactatemia and Normal Central Venous Oxygen Saturation

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Abstract

Background: After cardiac surgery, central venous oxygen saturation ($ScvO_2$) and serum lactate concentration are often used to guide resuscitation; however, neither are completely reliable indicators of global tissue hypoxia. This observational study aimed to establish whether the ratio between the veno-arterial carbon dioxide and the arterial-venous oxygen differences ($P(v-a)CO_2/C(a-v)O_2$) could predict whether patients would respond to resuscitation by increasing oxygen delivery (DO_2).

Methods: We selected 72 patients from a cohort of 290 who had undergone cardiac surgery in our institution between January 2012 and August 2014. The selected patients were managed postoperatively on the Intensive Care Unit, had a normal $ScvO_2$, elevated serum lactate concentration, and responded to resuscitation by increasing DO_2 by >10%. As a consequence, 48 patients responded with an increase in oxygen consumption (VO_2) while VO_2 was static or fell in 24.

Results: At baseline and before resuscitative intervention in postoperative cardiac surgery patients, a $P(v-a)CO_2/C(a-v)O_2$ ratio ≥1.6 mmHg/ml predicted a positive VO_2 response to an increase in DO_2 of >10% with a sensitivity of 68.8% and a specificity of 87.5%.

Conclusions: $P(v-a)CO_2/C(a-v)O_2$ ratio appears to be a reliable marker of global anaerobic metabolism and predicts response to DO_2 challenge. Thus, patients likely to benefit from resuscitation can be identified promptly, the $P(v-a)CO_2/C(a-v)O_2$ ratio may, therefore, be a useful resuscitation target.

Key words: Cardiac Surgical Procedures; Lactic Acid; Physiologic Monitoring; Resuscitation

Introduction

Hyperlactatemia is common after cardiac surgery. Impaired tissue oxygenation leads to increased anaerobic metabolism and production of pyruvate, which is subsequently converted to lactate. Numerous studies have established the use of serum lactate concentration as a marker of global tissue hypoxia in circulatory shock, but after cardiac surgery hyperlactatemia may occur as a result of other mechanisms, such as the stress response to surgery and the use of β-adrenergic,[1,2] and other diseases also have reported, such as sepsis.[3,4] Therefore, after cardiac surgery, hyperlactatemia may not be a reliable means of judging the adequacy of tissue oxygenation.

A normal central venous oxygen saturation ($ScvO_2$) generally indicates that oxygen delivery (DO_2) is sufficient to meet oxygen consumption (VO_2), and further increasing DO_2 is not necessary. A persistently normal $ScvO_2$ and decreasing serum lactate concentration normally reflects a resolving oxygen deficit, and that any oxygen debt is being repaid. Nevertheless, $ScvO_2$ may not reflect tissue hypoxia when VO_2 is impaired by mitochondrial dysfunction or cytopathic hypoxia,[5] or when microcirculatory failure results in shunting of blood away from metabolically active but hypoxic tissues.[6] Therefore, neither $ScvO_2$ nor serum lactate concentration can be completely relied upon to detect

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clinically important anaerobic metabolism. It may not be clear how to manage cardiac surgical patients with a normal $ScvO_2$ and hyperlactatemia, and the inappropriate use of excessive volume expansion or positive inotropic agents carries substantial risks.

It is important, therefore, to find reliable indices to predict when an increase in DO_2 will reduce the oxygen debt, reflected by an increase in VO_2. A recent study showed that the ratio between veno-arterial carbon dioxide difference and arterial-venous oxygen difference ($P(v-a)CO_2/C(a-v)O_2$) is a hallmark of oxygen deficit caused by acute circulatory failure.[7]

As oxygen supply dependency, reflected by derangements in the relationship between VO_2 and DO_2, is a hallmark of acute circulatory failure.[8] We hypothesized that $P(v-a)\ CO_2/C(a-v)O_2$ can be used as an index of global tissue hypoxia in cardiac surgery patients. We undertook serial measurements of VO_2 because DO_2 changed after cardiac surgery to illuminate the relationship between the two parameters.

Methods

We prospectively collected the data of a cohort of consecutive adults who underwent cardiac surgery between January 2012 and August 2014 at the Peking Union Medical College Hospital (PUMCH), and were admitted to the 15-bed general Intensive Care Unit (ICU) for postoperative care. The Institutional Research and Ethics Committee of the PUMCH approved this study for human subjects. Because the laboratory tests undertaken and the data collected were part of routine clinical practice, the study was observational and thus informed consent was not required.

Patients

We collected data from patients with hyperlactatemia and normal $ScvO_2$, and in whom changes in therapy during the first 6 h of postoperative care resulted in changes in DO_2. During the study period, 290 patients after cardiac surgery were admitted to the ICU and received pulse contour continuous cardiac output (PiCCO) monitoring (PiCCO; Pulsion Medical Systems, Munich, Germany). Indications for PiCCO catheterization were: Left ventricular ejection fraction <45%; history of myocardial infarction; resection of a ventricular aneurysm; repeat coronary artery bypass grafting; left main or complex coronary artery disease; replacement of two valves; and hemodynamic instability. Two hundred and twenty-one were found to have hyperlactatemia and normal $ScvO_2$. Inclusion criteria were: A serum lactate concentration >2 mmol/L; $ScvO_2$ >60.8% on admission to the ICU (considered the normal $ScvO_2$ for cardiac surgical patients);[9] and resuscitation that resulted in changes in DO_2 of >10%.[8]

The interventions made to improve the DO_2 were chosen at the discretion and clinical judgment of the attending physicians. Of the 221 patients, interventions were made to improve DO_2 in 123; the remaining 98 were managed supportively and observed for improvement in serum lactate concentration. Of those patients in whom an intervention was made, an improvement of DO_2 ≥10% was only seen in 72 (58.5%). A patient flow chart is shown in Figure 1.

Measurements

Arterial pressure and heart rate were monitored continuously using a femoral artery catheter and the PiCCO plus device (Pulsion Medical Systems, Munich, Germany). Clinical strategies to improve DO_2 included intravenous fluid challenges and the use of positive inotropic agents. If the stroke volume variation (SVV) (measured in patients in sinus rhythm who were mechanically ventilated and fully adapted to the ventilator settings) exceeded 13%, a fluid challenge was given until the SVV fell below 13%. Thereafter, if the cardiac index (*CI*) was <2.5 $L\cdot min^{-1}\cdot m^{-2}$, dobutamine, milrinone or epinephrine was administered as an intravenous infusion to achieve a *CI* >2.5 $L\cdot min^{-1}\cdot m^{-2}$. The doses of inotropes were moderated in the presence of cardiac arrhythmia. If there was severe hypotension (systolic blood pressure ≤60 mmHg), norepinephrine was administered as an intravenous infusion, but the dose titrated so that the systemic vascular resistance index (SVRI) did not exceed 2500 $dyn\cdot s^{-1}\cdot cm^{-5}\cdot m^{-2}$. After each intervention, *CI*, stroke volume index, global end-diastolic volume index (GEDVI), and SVRI were measured using a transpulmonary thermodilution technique with the mean cardiac output (CO) of three measurements within 10% of each other used to calculate each variable. All measurements were undertaken in a stable environment in the absence of any other intervention likely to alter oxygen demand or delivery, such as changes in sedation, physiotherapy, and tracheobronchial toilet. Arterial and central venous blood samples were taken for measurement of acid-base status (Abl 3 Automated Blood Gas Analyzer, Radiometer, Copenhagen, Denmark), hemoglobin (Hb) concentration, and oxygen saturation (Hemoximeter, OSM 3, Radiometer, Copenhagen, Denmark). Arterial lactate concentrations were determined enzymatically (Hitachi Analyzer, Tokyo, Japan). The normal blood lactate value for our laboratory was <2.0 mmol/L. Oxygen-derived variables were calculated using standard formulae. Veno-arterial carbon dioxide difference ($P(v-a)CO_2$) and the ratio of $P(v-a)CO_2/C(a-v)O_2$ were calculated using the following formulae:

$$P(v-a)CO_2 = PvCO_2 - PaCO_2.$$

$$\text{Ratio} = P(v-a)CO_2/(CaO_2-CvO_2).$$

The anion gap (AG) was calculated as follows:
$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$ and corrected for the effect of abnormal albumin concentration thus: Corrected anion gap (AGcorrected) (mmol/L) = AG + 0.25× (normal albumin − observed albumin) (g/L).[10]

Finally, we divided patients who responded to interventions to improve DO_2 into two groups on the basis of the resultant change in VO_2: In the first group, an improvement in VO_2

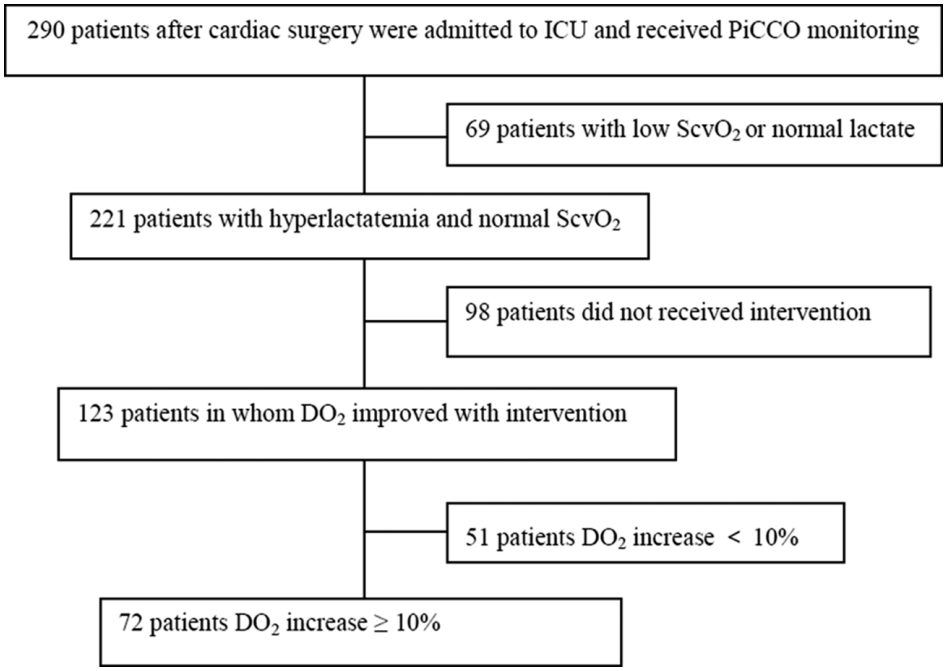

Figure 1: Study flow chart. PiCCO: Pulse contour continuous cardiac output; $ScvO_2$: Central venous oxygen saturation; DO_2: Oxygen delivery.

was observed (ΔVO_2 >0%, the "VO_2 increase group"); in the second VO_2 remained unchanged or declined (ΔVO_2 ≤0% the "VO_2 no-increase group").

Statistical analysis

A descriptive analysis was undertaken. All normally distributed data were expressed as the mean ± standard deviation (SD) unless otherwise specified. Differences between baseline variables and those recorded after intervention in the two groups were tested for statistical significance using the independent-samples *t*-test for continuous data and the Chi-square test for categorical variables. All comparisons were two-tailed, and $P < 0.05$ was required to exclude the null hypothesis. We also constructed receiver operator characteristic (ROC) curves to test the ability of the $P(v-a)CO_2/C(a-v)O_2$ ratio at baseline to predict an increase in VO_2 in patients in whom DO_2 responded to intervention. The areas under the ROC curves (AUCs) are expressed as mean (95% confidence interval [*CI*]) and were compared using the Hanley–McNeil test. All statistical analyses were undertaken using the SPSS software package (version 13.0, SPSS, Chicago, IL, USA).

Results

Seventy-two patients admitted the ICU after cardiac surgery fulfilled the inclusion criteria [Figure 1]. On admission, their mean baseline $ScvO_2$ was 75.3% ± 6.9% and serum lactate concentration 5.6 ± 3.1 mml/L; their demographic and physiological data and outcomes are shown in Table 1.

Clinical management

Improvements in DO_2 were achieved using one or more of the following strategies: Intravenous fluid challenge ($n = 58$); dobutamine ($n = 9$), milrinone ($n = 36$) or epinephrine ($n = 58$) infusion; blood transfusion ($n = 9$); or an increase the positive end-expiratory pressure ($n = 2$). Data from the 72 patients demonstrated that changes in VO_2 (101 ± 35 vs. 126 ± 47 $ml \cdot min^{-1} \cdot m^{-2}$; $P = 0.003$) paralleled changes in DO_2 (438 ± 139 vs. 531 ± 159 $ml \cdot min^{-1} \cdot m^{-2}$; $P < 0.001$). Of the patients in whom DO_2 improved by >10%, VO_2 improved in 48 patients (ΔVO_2 >0%), but not in 24 (ΔVO_2 ≤0%).

Differences between the oxygen consumption (VO_2) increase and VO_2 no-increase groups

There were no significant differences between the groups in terms of baseline patient characteristics, such as acute physiology and chronic health evaluation II scores, preoperative ejection fraction, and New York Heart Association functional heart failure class. There were also no differences in terms of surgery characteristics, such as cardiopulmonary bypass (CPB) time and aortic cross-clamping time. There were also no significant physiological differences between the groups, such as the lowest mean arterial pressure during CPB, the highest serum lactate concentration, the lowest base excess, the lowest serum bicarbonate concentration or the volume of blood transfused. Finally, there were no significant differences in the need for postoperative vasopressor and inotropic agents [Table 2].

At baseline, there were significant differences in $P(v-a)CO_2/C(a-v)O_2$ ratio and VO_2 between the groups (2.2 ± 1.2 vs. 1.2 ± 0.4 mmHg/ml, $P = 0.030$ and 88.6 ± 28.5 vs. 130.3 ± 32.4 $ml \cdot min^{-1} \cdot m^{-2}$, $P = 0.004$, respectively); however, there were no significant differences in hemodynamic (such as central venous pressure [CVP], *CI*, GEDVI, SVRI and extravascular lung water index), global metabolic (such as DO_2 and oxygen extraction ratio [ERO_2]) or tissue perfusion parameters [such as $ScvO_2$, $P(v-a)CO_2$, serum lactate and AGcorrected; Table 3]. After

Table 1: Characteristics of patients after cardiac surgery

Characteristics	Values
Age (mean ± SD), years	54 ± 19
Sex (male/female), *n*	42/30
Body mass index (mean ± SD), kg/m^2	23.5 ± 3.0
APACHE II score (mean ± SD)	19.6 ± 8.6
Type of surgery, *n*	
Coronary artery bypass graft	27
Valve replacement	33
Aortic	18
Mitral	12
Aortic + mitral	3
Pulmonary endarterectomy	4
Resection of cardiac tumor	6
Fontan procedure	2
Preoperative ejection fraction, %	58.3 ± 14.9
Preoperative creatinine, μmol/L	59.5 (53.5-98.8)
History, *n* (%)	
Previous myocardial infarction	18 (25)
Hypertension	33 (45.8)
Diabetes	30 (41.7)
Cerebrovascular disease	15 (20.8)
Peripheral vascular disease	3 (4.2)
Emergency surgery, *n* (%)	48 (66.7)
Preoperative cardiac shock, *n* (%)	3 (4.2)
Use of IABP preoperatively, *n* (%)	3 (4.2)
Use of IABP surgery, *n* (%)	15 (20.8)
Use of IABP after surgery, *n* (%)	9 (12.5)
Patients receiving vasopressor	
Norepinephrine, *n* (%)	57 (79.2)
Norepinephrine dose (mean ± SD), μg·kg^{-1}·min^{-1}	0.39 ± 0.40
Patients receiving inotropic agent	
Dobutamine, *n* (%)	9 (12.5)
Dobutamine dose (mean ± SD), μg·kg^{-1}·min^{-1}	2.99 ± 2.56
Epinephrine, *n* (%)	54 (75)
Epinephrine dose (mean ± SD), μg·kg^{-1}·min^{-1}	0.24 ± 0.53
Milrinone, *n* (%)	36 (50)
Milrinone dose (mean ± SD), μg·kg^{-1}·min^{-1}	0.37 ± 0.20
DO_2 (mean ± SD), ml·min^{-1}·m^{-2}	438.2 ± 138.6
VO_2 (mean ± SD), ml·min^{-1}·m^{-2}	102.5 ± 35.4
ERO_2, %	24.6 ± 9.4
$ScvO_2$, %	75.3 ± 6.9
Lactate (mean ± SD), mmol/L	5.6 ± 3.1
$P(v-a)CO_2$ (mean ± SD), mmHg	5.8 ± 2.5
$P(v-a)CO_2/C(a-v)O_2$ ratio (mean ± SD), mmHg/ml	1.9 ± 1.1
AGcorrected (mean ± SD), mmol/L	18.8 ± 4.5
Length ICU stay, days	8.9 ± 5.7
Length hospital stay, days	42.8 ± 20.9
Mortality at day 28, %	16.7

APACHE II: Acute physiological and chronic health evaluation II score; IABP: Intra-aortic balloon pump; DO_2: Oxygen delivery; VO_2: Oxygen consumption; ERO_2: Oxygen extraction ratio; $ScvO_2$: Central venous oxygen saturation; AGcorrected: Corrected anion gap; $P(v-a)CO_2$: Veno-arterial carbon dioxide difference; $C(a-v)O_2$: Arterial-venous oxygen difference; ICU: Intensive Care Unit; SD: Standard deviation.

intervention, there was a significant difference in $ScvO_2$ between the groups (73.5% ± 6.4% vs. 79.2% ± 5.7%, $P = 0.043$), but not in any of the other hemodynamic, global metabolic or tissue perfusion variables [Table 3].

In the VO_2 increase group, DO_2 increased by 23% ± 13% ($P < 0.001$) and VO_2 by 46% ± 38% ($P < 0.001$). The intervention to increase DO_2 by >10% significantly altered CVP (9.5 ± 3.3 vs. 12.1 ± 3.5 mmHg, $P < 0.001$), *CI* (3.0 ± 0.8 vs. 3.7 ± 1.0 L·min^{-1}·m^{-2}, $P < 0.001$), SVRI (2106.7 ± 954.1 vs. 1565.9 ± 572.3 dyn·s^{-1}·cm^{-5}·m^{-2}, $P = 0.002$), ERO_2 (22.7% ± 7.7% vs. 26.0% ± 7.2%, $P = 0.047$) and $P(v-a)CO_2/C(a-v)O_2$ ratio [2.2 ± 1.2 vs. 1.2 ± 0.8 mmHg/ml, $P = 0.013$; Table 3]. In the VO_2 no-increase group, even though DO_2 increased by 21% ± 11% (497.8 ± 154.4 vs. 594.9 ± 162.4 ml·min^{-1}·m^{-2}, $P < 0.001$), VO_2 fell by 7% ± 10% (130.3 ± 32.4 vs. 118.4 ± 37.9 ml·min^{-1}·m^{-2}, $P = 0.086$). Nonetheless, there were significant changes in CVP (9.3 ± 2.0 vs. 11.4 ± 3.7 mmHg, $P = 0.018$), *CI* (3.2 ± 0.7 vs. 3.9 ± 0.6 L·min^{-1}·m^{-2}, $P < 0.001$) and $ScvO_2$ (73.4% ± 7.4% vs. 79.2% ± 5.7%, $P = 0.015$) after intervention to improve DO_2 [Table 3].

Baseline prediction of an oxygen consumption response to improved oxygen delivery

A baseline $P(v-a)CO_2/C(a-v)O_2$ ratio ≥1.6 mmHg/ml predicted an improvement in VO_2 when DO_2 increased by >10%, with a sensitivity of 68.8% and a specificity of 87.5%. The AUC was 0.77 ± 0.10 [$P = 0.032$; Figure 2]. No other variable, including $ScvO_2$, serum lactate or AGcorrected, significantly predicted a VO_2 response [Table 3].

Discussion

Our main finding was that the $P(v-a)CO_2/C(a-v)O_2$ ratio was a reliable marker of global anaerobic metabolism in cardiac surgery patients and predicts whether improved DO_2 will result in an increase in VO_2. This is particularly helpful in guiding the management of patients after cardiac surgery, when hyperlactatemia might not always represent anaerobic metabolism, and a normal $ScvO_2$ may fail to reflect persistent tissue hypoxia.[6] However, care must be exercised when seeking to elevate CO to improve DO_2 in patients who have undergone cardiac surgery. The $P(v-a)CO_2/C(a-v)O_2$ ratio allows patients likely to respond to intervention to be treated appropriately without exposing those who will not to unnecessary risk. At baseline in postoperative cardiac surgery patients, a $P(v-a)CO_2/C(a-v)O_2$ ratio ≥1.6 mmHg/ml predicted a positive VO_2 response when DO_2 was increased by >10%, with a sensitivity of 68.8% and a specificity of 87.5%. This finding is consistent with another recent study that found that a cut-off of 1.8 mmHg/ml had a reasonable sensitivity and specificity to predict VO_2 response.[7]

Physiological relevance of the $P(v-a)CO_2/C(a-v)O_2$ ratio

The $P(v-a)CO_2/C(a-v)O_2$ ratio positively correlates with the respiratory quotient (RQ). According to the Fick equation, VO_2 is the product of CO and arteriovenous O_2 content difference ($C(a-v)O_2$). Carbon dioxide production (VCO_2) is equal to the product of CO and veno-arterial CO_2 content difference. Under most normal physiological circumstances, CO_2 tension is linearly related to CO_2 content, so an

Table 2: Physiological and surgical characteristics of the VO_2 increase and VO_2 no-increase groups

Characteristics	VO_2 increase group (n = 48)	VO_2 no-increase group (n = 24)	P
APACHE II scores on admission to ICU (mean ± SD)	18.6 ± 8.5	21.4 ± 8.8	0.460
Preoperative left ventricular ejection fraction, %	57.5 ± 16.4	60.1 ± 12.1	0.706
Preoperative NYHA heart failure class, *n*			
I	0	3	0.502
II	15	6	
III	24	9	
IV	9	6	
The percentage of accepted CPB	100	100	
CPB time, min	114.4 ± 47.6	116.4 ± 32.9	0.916
Aortic cross-clamp time, min	72.8 ± 34.2	79.5 ± 27.8	0.634
Lowest MAP during CPB, mmHg	60.6 ± 12.1	60.5 ± 8.2	0.979
Blood transfusion during surgery (median [IQR]), units	4 [0–4]	4 [2.25–5.50]	0.312
Lowest lactate during CPB (mean ± SD), mmol/L	5.3 ± 3.4	4.9 ± 2.1	0.785
Lowest base excess during CPB (mean ± SD), mmol/L	−4.4 ± 3.0	−4.3 ± 2.2	0.927
Lowest bicarbonate during CPB (mean ± SD), mmol/L	21.3 ± 1.9	22.0 ± 1.6	0.4
Postoperative ejection fraction at 2 weeks, %	57.7 ± 14.7	61.6 ± 13.1	0.567
Number of patients receiving a vasopressor			
Norepinephrine, *n* (%)	39 (81.2)	18 (75.0)	0.722
Norepinephrine dose (mean ± SD), $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.39 ± 0.43	0.37 ± 0.37	0.907
Number of patients receiving an inotropic agent			
Dobutamine, *n* (%)	9 (18.8)	0 (0)	0.190
Dobutamine dose (mean ± SD), $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.99 ± 2.56		
Epinephrine, *n* (%)	33 (68.8)	21 (87.5)	0.317
Epinephrine dose (mean ± SD), $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.11 ± 0.09	0.44 ± 0.84	0.207
Milrinone, *n* (%)	21 (43.8)	15 (62.5)	0.386
Milrinone dose (mean ± SD), $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.40 ± 0.23	0.32 ± 0.16	0.524
Lactate clearance, %	10.2 ± 31.5	8.6 ± 18.2	0.897
Length of ICU stay, days	9.8 ± 6.3	7.0 ± 3.8	0.263
Length of hospital stay, days	42.8 ± 21.2	42.8 ± 21.8	0.995
Mortality at day 28, %	12.5	25.0	0.439

APACHE II: Acute physiological and chronic health evaluation II score; NYHA: New York Heart Association; CPB: Cardiopulmonary bypass; MAP: Mean arterial pressure; IQR: Interquartile range; ICU: Intensive Care Unit; SD: Standard deviation; VO_2: Oxygen consumption.

Table 3: Hemodynamic and metabolic variables of the VO_2 increase and VO_2 no-increase groups

Variables	VO_2 increase group (n = 48)		VO_2 no-increase group (n = 24)	
	Baseline	After intervention	Baseline	After intervention
CVP (mean ± SD), mmHg	9.5 ± 3.3‡	12.1 ± 3.5	9.3 ± 2.0§	11.4 ± 3.7
GEDVI (mean ± SD), ml/m^2	664.1 ± 190.9	686.5 ± 167.0	672.5 ± 329.4	722.3 ± 333.7
CI (mean ± SD), $L \cdot min^{-1} \cdot m^{-2}$	3.0 ± 0.8‡	3.7 ± 1.0	3.2 ± 0.7§	3.9 ± 0.6
SVRI (mean ± SD), $dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$	2106.7 ± 954.1‡	1565.9 ± 572.3	2106.0 ± 711.2	1648.9 ± 594.0
EVLWI (mean ± SD), ml/kg	7.7 ± 2.5	7.3 ± 2.4	9.1 ± 5.5	10.1 ± 6.1
DO_2 (mean ± SD), $ml \cdot min^{-1} \cdot m^{-2}$	408.5 ± 124.9‡	499.4 ± 151.9	497.8 ± 154.4§	594.9 ± 162.4
VO_2 (mean ± SD), $ml \cdot min^{-1} \cdot m^{-2}$	88.6 ± 28.5*‡	129.3 ± 51.9	130.3 ± 32.4	118.4 ± 37.9
ERO_2, %	22.7 ± 7.7‡	26.0 ± 7.2	28.3 ± 11.7	20.2 ± 5.3
$ScvO_2$, %	76.3 ± 6.7	73.5 ± 6.4†	73.4 ± 7.4§	79.2 ± 5.7
Lactate (mean ± SD), mmol/L	5.4 ± 3.1	4.9 ± 3.5	5.9 ± 3.3	5.5 ± 3.1
$P(v\text{-}a)CO_2$ (mean ± SD), mmHg	6.2 ± 2.5	4.3 ± 2.9	4.9 ± 2.2	3.2 ± 2.6
$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (mean ± SD), mmHg/ml	2.2 ± 1.2*‡	1.2 ± 0.8	1.2 ± 0.4	1.1 ± 0.8
AGcorrected (mean ± SD), mmol/L	18.1 ± 5.1	18.2 ± 4.9	20.2 ± 3.0	19.0 ± 4.6

*$P < 0.05$ for the VO_2 increase group versus the VO_2 no-increase group at baseline; †$P < 0.05$ for VO_2 increase group versus VO_2 no-increase group after intervention; ‡$P < 0.05$ for the difference between baseline and intervention in the VO_2 increase group; §$P < 0.05$ for the difference between baseline and intervention in the VO_2 no-increase group. CVP: Central venous pressure; GEDVI: Global end diastolic volume index; CI: Cardiac index; SVRI: Systemic vascular resistance index; EVLWI: Extravascular lung water index; DO_2: Oxygen delivery; VO_2: Oxygen consumption; ERO_2: Oxygen extraction ratio; $ScvO_2$: Central venous oxygen saturation; $P(v-a)CO_2$: Veno-arterial carbon dioxide difference; AGcorrected: Corrected anion gap; SD: Standard deviation; $C(a\text{-}v)O_2$: Arterial-venous oxygen difference.

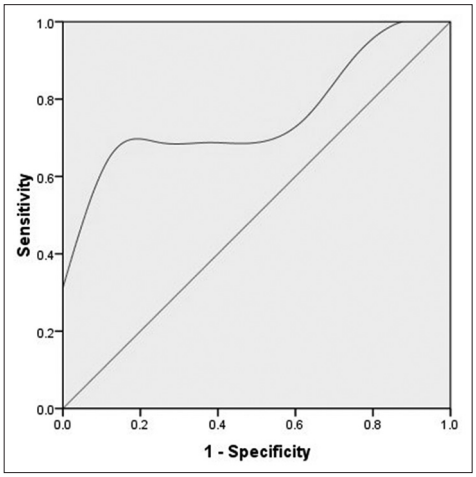

Figure 2: Receiver operating characteristic (ROC) curve. ROC curve comparing the $P(v-a)CO_2/C(a-v)O_2$ ratio to an increase in oxygen consumption (VO_2) brought about by increasing oxygen delivery (DO_2) by >10% in cardiac surgical patients. Area under the curve: 0.77 ± 0.10, $P = 0.032$, The cutoff of the $P(v-a)CO_2/C(a-v)O_2$ ratio value was 1.6 for predicting cardiac surgery patients in whom VO_2 would increase when DO_2 increased by >10%, resulting in a sensitivity of 68.8% and a specificity of 87.5%.

increase in the RQ should be reflected by an increase in the $P(v-a)CO_2/C(a-v)O_2$ ratio.[11]

During tissue hypoxia, the reduction in global O_2 consumption is accompanied by diminished aerobic but increased anaerobic CO_2 production, with excess protons buffered mostly by bicarbonate ions.[12] Thus, total VCO_2 should be reduced less than VO_2, hence, global anaerobic metabolism is reflected by increases in the RQ (VCO_2/VO_2) and $P(v-a)CO_2/C(a-v)O_2$ ratio.

Oxygen supply, demand and the $P(v-a)CO_2/C(a-v)O_2$ ratio

At baseline, we found that $P(v-a)CO_2/C(a-v)O_2$ ratio was higher in the VO_2increase group and predicted a response to resuscitation when $ScvO_2$ was normal, and serum lactate concentration was raised. Under these circumstances, hyperlactatemia equates with hypoxia. Friedman *et al*.[8] reported that interventions to increase DO_2 were justified when there was a VO_2 response, and the use of the $P(v-a)CO_2/C(a-v)O_2$ ratio is underpinned by the same pathophysiological concept. Outcomes are very poor in patients with an oxygen deficit whose VO_2 fails to respond to increased DO_2.[13] After cardiac surgery, the postoperative course is characterized by increases in cellular oxygen demand as a consequence of rising body temperature,[14] emergence from anesthesia, and the resumption of spontaneous ventilation.[15] Shivering, pain, and anxiety may further increase oxygen demand.[16] In complex situations, plotting VO_2/DO_2 over time during a DO_2 challenge allows the critical DO_2 to be identified. This ensures that VO_2 needs are met, a crucial objective even if DO_2 and VO_2 are estimated intuitively rather than measured directly. As DO_2 increases beyond the critical point, VO_2 may continue to rise slowly, rather than plateau. When oxygen requirements are excessive, DO_2 becomes uncoupled from metabolic activity;[17] as CO improves during a DO_2 challenge, the VO_2 of the muscles and viscera increase in direct proportion to blood flow.[18-20] Furthermore, additional oxygen is taken up by nonmitochondrial oxidase systems as dysoxia resolves.[21] It is therefore clinically important to be able to detect a VO_2 response to a DO_2 challenge, especially when the extent of oxygen deficit is unclear.

$P(v-a)CO_2/C(a-v)O_2$ ratio is superior to lactate and lactate clearance rate

Hyperlactatemia on admission to ICU after cardiac surgery was found to predict mortality in some single-center studies,[22,23] but not in larger studies.[24,25] Early after CPB, hyperlactatemia may reflect intraoperative factors rather than anaerobic metabolism, a concept supported by our findings. In our study, there were no significant differences in serum lactate concentrations between the groups at baseline, or before and after the intervention.

Hyperlactatemia may not be directly caused by tissue dysoxia. There is a delay of 30–60 min between myocardial reperfusion and normalization of lactate concentration measured in the coronary sinus, suggesting that anaerobic metabolism continues within the myocardium for some time after ischemia.[26] Restoration of blood flow in animal and human models of circulatory failure results in lactate "washout" from regional tissues, especially from the coronary and renal circulations.[1] Pulmonary lactate levels rise significantly after surgical trauma and CPB, and may contribute significantly to circulating lactate levels up to 6 h postoperatively.[27] It has been hypothesized that lactate is used as a source of energy during physiological stress.[6] When lactate remains high despite evidence that a VO_2 plateau has been reached, there is no evidence that increasing DO_2 further is beneficial,[13] and indeed could be harmful in patients with impaired cardiac function. We observed a trend that serum lactate concentration fell after intervention, even in the group that did not mount a VO_2 response, although the differences were not statistically significant. This could be explained by lactate "washout" or other factors. The kinetics of lactate clearance depends fundamentally on hepatic clearance, which appears to be preserved even during cardiogenic shock.[28]

Early recognition of shock is critical, as it responds better to intervention in the early stages,[29] and there is some evidence that rapidly achieving an adequate total body VO_2 is a prerequisite of successful resuscitation. Delaying resuscitation causes macro- and microcirculatory failure and ultimately cell necrosis, which cannot be corrected by resuscitation. In shock, the oxygen deficit is only a "snapshot" calculated as the difference between baseline "normal" VO_2 and the VO_2 measured at a particular time; however, oxygen debt accumulates over time. The $P(v-a)CO_2/C(a-v)O_2$ ratio can be measured as a "snapshot," whereas measuring lactate clearance rate takes time, during which patients may be exposed to prolonged periods of tissue hypoperfusion.

$P(v-a)CO_2/C(a-v)O_2$ ratio is superior to central venous oxygen saturation

An $ScvO_2$ <60.8% is considered unsatisfactory after cardiac surgery and can be found in approximately 13% of patients. In contrast, supranormal levels >77.4% occurs in approximately one-third of patients, and appears to be a warning sign of impaired tissue oxygenation and is associated with higher mortality.[9] Patients with low $ScvO_2$ and hyperlactatemia clearly require resuscitation, so we focused on patients with $ScvO_2$ >61%, where the situation is less clear. We did not, however, distinguish between patients with normal and supranormal $ScvO_2$ as the boundaries between the two are less well defined.

Assuming that "supranormal" $ScvO_2$ indicates impaired tissue oxygenation, there are three mechanisms that are likely responsible for the co-existence of normal or supranormal $ScvO_2$ and hyperlactatemia after cardiac surgery: CPB or off-pump surgery with concomitant mitochondrial dysfunction; therapeutic interventions to increase DO_2, most notably β-mimetics;[4] and macrocirculatory failure combined with microcirculatory or mitochondrial failure. In health, VO_2 is determined by the metabolic needs of the tissues and when DO_2 increases VO_2 remains relatively constant as the tissues adapt their ERO_2 accordingly, known as oxygen supply independency. In shock, however, mitochondrial dysfunction or microvascular shunting may result in persistent anaerobic metabolism and static VO_2 even as DO_2 improves with resuscitation. Oxygen extraction and SvO_2 (or $ScvO_2$) are linked by a simple equation: $ScvO_2 = 1 - ERO_2$, which can be rewritten as $ScvO_2 = 1 - VO_2/DO_2$ if it is assumed that $SaO_2 = 1$. Thus, if DO_2 is altered in the face of a relatively constant VO_2, $ScvO_2$ will increase, and ERO_2 will fall. We found that there was a significant rise in $ScvO_2$ in the VO_2 no-increase group after intervention, but our study was unable to distinguish between patients with mitochondrial dysfunction or microcirculatory shunt and those with oxygen supply independency. Even so, further macrocirculatory resuscitation is not warranted in either case and a single baseline measurement of $P(v-a)CO_2/C(a-v)O_2$ ratio appears to be superior to $ScvO_2$ in helping to identify patients likely to respond to intervention.

$P(v-a)CO_2/C(a-v)O_2$ ratio is superior to $P(v-a)CO_2$

Veno-arterial PCO_2 difference ($P(v\text{-}a)CO_2$) has been proposed to be a marker of tissue hypoxia, and is also often used to guide resuscitation.[30] However, it is not clear whether it reliably identifies VO_2 responders. Van der Linden *et al.* found a significant correlation between blood lactate levels and $P(v-a)CO_2$ in an animal model of acute hemorrhage,[31] and progressive increases in $P(v-a)CO_2$ have been observed during the VO_2/DO_2 dependent period as blood flow falls.[32]

Hypoperfusion can result in a widening of $P(v-a)CO_2$ even if no additional CO_2 production occurs, known as the CO_2-stagnation phenomenon. $P(v-a)CO_2$ could, therefore, be considered to be an indicator of adequate venous blood flow to remove CO_2 produced in the peripheries.[33] In the isolated dog limb model of hypoxia, Vallet *et al.* found that $P(v-a)CO_2$ was increased in ischemic hypoxia but not hypoxic hypoxia, suggesting that $P(v-a)CO_2$ has poor sensitivity for detecting tissue hypoxia.[34] $P(v\text{-}a)CO_2 = k \times VCO_2/CO$, where k is assumed to be constant. $VCO_2 = RQ \times VO_2$, $CO = DO_2/SaO_2 \times 1.34 \times Hb$. Comprehensive the above three equations, $P(v-a)CO_2 = RQ \times ERO_2 \times SaO_2 \times Hb \times k$. If arterial oxygen saturation (SaO_2) and Hb remain constant, $P(v\text{-}a)CO_2$ is influenced by RQ and ERO_2. A high ERO_2 (and hence low $ScvO_2$) is associated with increased mortality in the presence of high serum lactate concentration.[6]

Although high ERO_2 increases the numerical value of $P(v-a)CO_2$, it does not reliably reflect anaerobic metabolism as there is significant individual variation in the anaerobic threshold. We found trends to suggest that $P(v-a)CO_2$ was higher in the VO_2 increase group than the VO_2 no-increase group, and in the VO_2 increase group before and after intervention, but the differences were not statistically significant.

$P(v-a)CO_2/C(a-v)O_2$ ratio is superior to corrected anion gap

The corrected and strong ion gaps have been advocated as surrogate markers of global anaerobic metabolism, and deficits in DO_2 and cellular perfusion in cardiac critical care[35] and AG has been used as a therapeutic target in research.[36] Although the link between metabolic acidosis and tissue hypoperfusion is well-established, we found no relationship between AGcorrected and anaerobic metabolism as above.

Limitations

Our study has several limitations. First, myocardial ischemia and reperfusion injury and the effects of anesthetic drugs may limit tissue oxygen use and the CO response to DO_2 challenge.[37] In addition, resuscitation was not guided by the protocol but left to the discretion of the attending physician and thus ours is an observational study, albeit an observation of routine clinical practice. Second, only a small proportion of patients met our inclusion criteria, so our findings cannot be generalized to those in whom DO_2 did not respond to intervention or those with arrhythmia. A larger multi-center study will be needed to confirm our findings and determine more accurate ratio cutoff values. Third, hyperthermia, acute respiratory failure, and pain increase VO_2 needs sharply. Antipyretic drugs, sedation, and mechanical ventilation[38] can reduce VO_2 by up to 50%, so can have the same effect as doubling CO or ERO_2. When seeking to improve DO_2, it is also important to reduce VO_2, but we did not examine the benefits of interventions that decrease VO_2, instead we sought to identify patients able to mount a DO_2 response to resuscitation. After cardiac surgery hyperlactatemia does not always reflect anaerobic metabolism, and a normal $ScvO_2$ does not indicate that resuscitation has been adequate. We found that the $P(v-a)CO_2/C(a-v)O_2$ ratio appears to be a reliable marker of global anaerobic metabolism and predicts response to DO_2 challenge, suggesting that it may be a useful resuscitation target.

In conclusion, $P(v-a)CO_2/C(a-v)O_2$ ratio appears to be a reliable marker of global anaerobic metabolism and

predicts response to DO_2 challenge. Thus, patients likely to benefit from resuscitation can be identified promptly, and those in whom a VO_2 response is unlikely can be spared the unnecessary risks associated with fluid overload and positive inotropic drugs. The $P(v-a)CO_2/C(a-v)O_2$ ratio may, therefore, be a useful resuscitation target.

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