Associations between oxygen delivery and cardiac index with hyperlactatemia during cardiopulmonary bypass

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ABSTRACT

Objective: Metabolism management plays an essential role during cardiopulmonary bypass (CPB). There are different metabolic management devices integrated to heart–lung machines; the most commonly used and accepted metabolic target is indexed oxygen delivery (DO_{2i}) (280 mL/min/m^2) and cardiac index (CI) (2.4 L/min/m^2), which can be managed independently or according to other metabolic parameters. Our objective was to compare lactate production during CPB procedures using different metabolic management: DO_{2i} in relation to indexed oxygen extraction ratio (O_2ER_i) and CI in relation to mixed venous oxygen saturation (SvO_2).

Methods: Data on 500 CPB procedures were retrospectively collected in a specialized regional tertiary cardiac surgery center in Italy between September and 2012 and November 2019. In group A, the DO_{2i} with 280 mL/min/m^2 target in relation to O_2ER_i 25% was used; in group B, CI with 2.4 L/min/m^2 target in relation to SvO_2 75% was used. During CPB, serial arterial blood gas analyses with blood lactate and glucose determinations were obtained. Hyperlactatemia (HL) was defined as a peak arterial blood lactate concentration >3 mmol/L. The postoperative outcome of patients with or without HL was compared.

Results: Eight pre- and intraoperative factors were found to be significantly associated with peak blood lactate level during CPB at univariate analysis. HL (>3 mmol/L) was detected in 15 (6%) patients of group A and in 42 (16.8%) patients of group B ($P = .022$); hyperglycemia (>160 mg/dL) was found in 23 (9.2%) patients of group A and in 53 (21.2%) patients of group B ($P = .038$). Patients with HL during CPB had a significant increase in serum creatinine value, higher rate of prolonged mechanical ventilation time and intensive care unit stay. A cutoff of DO_{2i} <270 mL/min/m^2 in relation to O_2ER_i >35% in group A and a cutoff of CI <2.4 L/min/m^2 in relation to SvO_2 <65% in group B were found to have a positive predictive value of 80% and 75% for HL, respectively. A cutoff of DO_{2i} >290 mL/min/m^2 in relation to O_2ER_i 24% in group A and a cutoff of CI >2.4 L/min/m^2 in relation to SvO_2 >75% in group B were found to have a negative predictive value of 78% and 62% for HL, respectively.

Conclusions: This retrospective observational analysis showed that management of DO_{2i} in relation to O_2ER_i was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. Group A reported a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and intensive care unit stay, compared with group B. (JTCVS Techniques 2020;2:92-9)
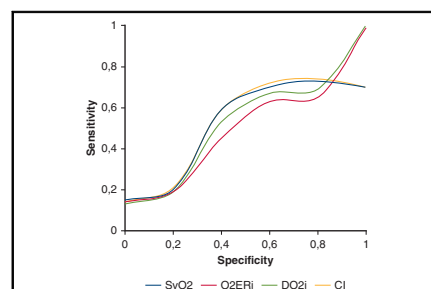
Sensitivity/specificity curves for cardiac index, indexed oxygen delivery, indexed oxygen extraction ratio, and mixed venous oxygen saturation.

CENTRAL MESSAGE

This study showed that management of indexed oxygen delivery in relation to indexed oxygen extraction ratio was more specific in terms of negative predictive value for hyperlactatemia during cardiopulmonary bypass compared with cardiac index and mixed venous oxygen saturation.

PERSPECTIVE

The management of indexed oxygen delivery in relation to indexed oxygen extraction ratio follow the cardiopulmonary bypass was more specific in terms of negative predictive value for hyperlactatemia compared to the use of cardiac index in relation to mixed venous oxygen saturation. That management can correlate with postoperative better outcome especially in terms of serum creatinine, mechanical ventilation time, and intensive care unit stay.

▶ Video clip is available online.

VIDEO 1. Ignazio Condello, PhD, summarizes the results of the study and explains the relevance of the research for the readers of the *Journal*. Video available at: https://www.jtcvs.org/article/S2666-2507(20)30189-9/fulltext.
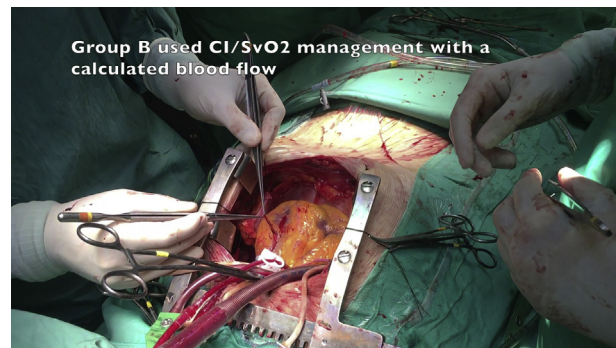
During cardiac surgery with cardiopulmonary bypass (CPB) in adult patients, hyperlactatemia (HL) is detectable at a considerable rate (10%-20%)[1,2] and is associated with post-operative morbidity and mortality.[1] At present, the nature of HL during and after cardiac operations is not totally clear, but the majority of authors[3-6] tend to attribute this finding to tissue hypoxia (type A HL) even if type B HL (without tissue hypoxia) has been advocated in some cases.[7-9] The main factors leading to a possible organ dysoxia during CPB are the hemodilution degree[10] and a low peripheral oxygen delivery.[1,2,4-6,10-12] In the state of perfusion, there are different metabolic management devices integrated to the heart–lung machine (eg, Quantum Spectrum [Spectrum Medical, Cheltenham, England], Connect Livanova [London, England], CDI Terumo Medical, Vaughan, Ontario, Canada], Landing Eurosets [Medolla, Italy]), with multiple measured and calculated parameters; the most commonly used and accepted metabolic target for the scientific community is the value of indexed oxygen delivery (DO$_{2i}$) (280 mL/min/m^2) and the cardiac index (CI) (2.4 L/min/m^2). These parameters can be managed independently or according to other metabolic parameters (eg, hemoglobin [Hb], vascular resistance, temperature, and diuresis), resulting in wide variability in CPB management of each center.

This study has the objective to compare lactate production during CPB procedures using different metabolic management: DO$_{2i}$ in relation to indexed oxygen extraction ratio (O$_2$ER$_i$) (group A), and CI in relation to mixed venous oxygen saturation (SvO$_2$) (group B) (Video 1).

MATERIALS AND METHODS
Population and Study Design
This study presents a comparative retrospective analysis that has been carried out between 2 historical times: the first historical period (2012-2015) used conventional extracorporeal circulation with blood gas test for metabolic management during CPB; the second historical period (2016-2019) used conventional extracorporeal circulation with blood gas test and the integration with metabolic parameter monitoring system. Between September 2012 and November 2019, 500 adults aged >28 to 80 years were collected for elective cardiac surgery procedures, without chronic kidney failure and with calculated European System for Cardiac Operative Risk Evaluation II score (mean value, 4.1%-4.5%) at our institution (Department of Cardiothoracic Surgery, Anthea Hospital, Bari, Italy). The study protocol was approved by the local ethics committee and all patients provided written consent to scientific treatment of their data. Patients were divided into 2 groups for CPB metabolic management: in group A (study group, n = 250), the DO$_{2i}$ target with a target of 280 mL/min/m^2 was used in relation to O$_2$ER$_i$; in group B (control group, n = 250), the CI target with a target of 2.4 L/min/m^2 was used in relation to SvO$_2$.

Data Collection
Patients were selected according to the following criteria:

- Elective, primary cardiac surgery: complete CPB and cardioplegic arrest had to be foreseen with an expected CPB duration >90 minutes.
- Patients were excluded if they presented abnormal plasma lactate levels (>2 mmol/L) before entering CPB, renal or liver failure, obesity, uncompensated diabetes, autoimmune disease, active infection, any immunosuppressant therapy, or coagulation disorder. Patients undergoing surgery with circulatory arrest or having preoperative hematocrit (Hct) <27% were also excluded.

The cardiac surgery procedures that were analyzed for this study are coronary artery bypass graft (n = 200), isolated aortic valve replacement (n = 100) and mitral valve repair with minimally invasive approach (n = 200).

Preoperative data included patient demographic characteristics, baseline serum creatinine levels, ventricular ejection fraction, comorbidities (eg, chronic obstructive pulmonary disease or previous cerebrovascular accident), baseline Hb, logistic European System for Cardiac Operative Risk Evaluation II score and New York Heart Association functional class.[2]

Perioperative data included type of operation, CPB duration, nadir body temperature during CPB, nadir Hct and Hb values (measured at the start of the CPB operation and every 20 minutes thereafter), nadir DO$_{2i}$, nadir DO$_{2i}$/O$_2$ER$_i$ ratio during CPB, nadir CI, nadir CI/SvO$_2$, peak serum lactate, and glucose during CPB. Postoperative data included peak serum creatinine, mechanical ventilation time, and days spent in the intensive care unit (ICU).

The primary end points were specificity and sensitivity, positive and negative predictive value for HL between target DO$_{2i}$ in relation to O$_2$ER$_i$ during CPB compared with the control group in terms of

TABLE 1. Preoperative profile and operative data

Characteristic	Group A (n = 250)	Group B (n = 250)
Mean age (y)	69.6	71.3
Male sex	110 (44)	121 (48)
Mean body surface area (m^2)	1.75	1.79
Mean left ventricular ejection fraction (%)	46	48
Median NYHA functional class	2	2
EuroSCORE II (mean)	4.1	4.7
Pre-CPB hematocrit (%)	32.4 ± 1.2	32.6 ± 1.9
Pre-CPB Hb (g/dL)	10.4 ± 1.1	10.8 ± 1.2
No. of chronic obstructive pulmonary disease cases (mean)	23	24
Creatinine (mg/dL)	1.09 ± 0.6	1.06 ± 0.9
Obstructive coronary artery disease (%)	23	24

Values are presented as n (%), or mean ± standard deviation. *NYHA*, New York Heart Association; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *CPB*, cardiopulmonary bypass; *Hb*, hemoglobin.

intraoperative lactate and glycemia trends. Secondary end points were peak postoperative serum creatinine level,[13,14] mechanical ventilation time, and length of ICU stay.

Anesthetics and Surgical Procedures

Patients were monitored with 5-lead electrocardiography, a left radial artery catheter, capnography, pulse oximetry, and rectal/urine bladder temperature sensors. Transesophageal echocardiography was performed in all patients. Anticoagulant therapy consisted of heparin sodium before CPB at 300 IU/kg to give an activated clotting time of >480 seconds (ACT PLUS; Medtronic, Minneapolis, Minn); for antagonization of heparin, 0.5 to 0.75 mg protamine was applied for every 100 U heparin. Anesthesia was induced with intravenous sufentanil (0.5-1 μg/kg) and midazolam (0.08-0.2 mg/kg), and tracheal intubation was facilitated with intravenous rocuronium (0.6-1 mg/kg). Anesthesia was maintained with propofol (2-5 mg/kg) and sufentanil (0.5-2.0 μg/kg), and the depth of anesthesia was monitored using bispectral index values (BIS XP; Aspect Medical System, Newton, Mass). The dose of propofol was titrated to maintain bispectral index values between 40 and 60. Aortic valve replacement and coronary artery

bypass graft procedures were performed in median sternotomy with central cannulation, MVR in right minithoracotomy approach with peripheral cannulation, and surgical procedures were performed as routine by 2 surgeons. Concentrated red blood cells were transfused whenever Hb concentrations fell below 6 g/dL during surgery or below 8 g/dL during ICU stay.

CPB Setting

Both open (Admiral; Remo-well Eurosets; EOS Dideco; Mirandola, Italy; Inspire 6F; LivaNova) and closed circuits (Closed Eurosets) were used for CPB. Pericardial blood was collected separately and could be processed or reinjected, if needed. The hard shell and soft shell reservoir, oxygenating module and circuits were treated with phosphorylcholine (Agile Eurosets; P.hisio. LivaNova). All patients were treated with mild hypothermic CPB (34°C-36°C); a volume of 1250 mL crystalloid Ringer acetate solution was used for priming. The surgical procedures selected for this study do not justify the use of moderate hypothermia by falling below 34°C. For this reason, in the event of an initial increase in anaerobic metabolism, the first compensation approach was not to lower the temperature but possibly liquids or red blood cells were integrated.

The hardware consisted of a Stöckert S5 heart-lung machine and a Stöckert Heater Cooler System 3T (LivaNova) and the same cannulae were employed in both groups. For the administration of myocardial protection, a closed circuit for cardioplegia with heat exchanger, with an infusion syringe pump in series and Saint Thomas solution with procaine were used and repeated every 30 minutes. Group A used the Landing monitoring system (Eurosets) for DO_2 management during CPB. In both groups, blood gas analyses were performed using alpha-stat management with a blood-gas analyzer (GEM Premier 3000 IQM; Instrumentation Laboratory, Werfen Group IVD company, Munich, Germany) set to measure at 37°C.[4] On the basis of arterial blood data, we assessed the lowest Hct (percentage) on CPB; every 20 minutes, an arterial blood gas analysis, including blood glucose and lactate determination, was obtained. An Hb value <6 to 7 g/dL during CPB was considered the trigger point for red blood cell transfusion. All patients received tranexamic acid according to the routine protocol. Mean arterial pressure during CPB procedures was managed for values between 55 and 70 mm Hg.

Metabolic Management During CPB in Group A

In group A, DO_{2i} with a target of 280 mL/min/m^2 was managed in relation to O_2ER_i (the cutoff for increase in DO_{2i} was >25% O_2ER_i, the cutoff for decrease in DO_{2i} was <25% O_2ER_i). DO_{2i} and O_2ER_i-related measurements were performed using a Landing system provided by Eurosets. Data were collected every 5 seconds during CPB. Data required to calculate

TABLE 2. Operative data

Parameter	Group A (n = 250)	Group B (n = 250)	P value
CPB time (min)	125 ± 13.2	120 ± 8.37	.92
Aortic crossclamp time (min)	61 ± 4	68 ± 7	.75
Nadir temperature (°C) during CPB	34.9 ± 1.1	34.7 ± 2.1	.75
Nadir hemoglobin value (mg/dL) during CPB	8.73 ± 1.53	8.89 ± 1.25	.88
Nadir hematocrit (%) during CPB	25.6 ± 3.8	25.9 ± 3.1	.89
Nadir DO_{2i} (mL/min/m^2) during CPB	290 ± 29	278 ± 14	.039
O_2ER_i (%) during CPB	24 ± 1	29 ± 5	.0029
Nadir CI (L/min/m^2) during CPB	2.6 ± 0.2	2.4 ± 0.1	.0032
Nadir SvO_2 (%)	81 ± 2	70 ± 5	.0029

Values are presented as mean ± standard deviation. *CPB*, Cardiopulmonary bypass; DO_{2i}, indexed oxygen delivery; O_2ER_i, indexed oxygen extraction ratio; *CI*, cardiac index; SvO_2, mixed venous oxygen saturation.

TABLE 3. Univariate analysis (correlation matrix)

Factor	Correlation coefficient	P value
Age (y)	−0.079	.029
Isolated coronary operation	−0.075	.039
Lowest temperature on CPB	−0.219	.001
Lowest hematocrit on CPB	−0.149	.001
CPB duration	0.049	.001
Lowest pump flow	−0.239	.001
CPB lowest DO_{2i}	−0.254	.001
CPB peak blood glucose	0.497	.001

CPB, Cardiopulmonary bypass; DO_{2i}, indexed oxygen delivery.

DO_{2i} and O_2ER_i were arterial Hb; measured parameters included arterial saturation, SvO_2, blood pump flow, Hb, arterial and venous temperature, mean arterial pressure, body surface area, and CI.

DO_{2i} was calculated using the following equation:

$$DO_{2i}(mL/min/m^2) = 10 \times pump\ flow(L/min/m^2) \times$$

$$arterial\ O_2\ content(mL/100mL),$$

where arterial O_2 content was calculated as follows: (CaO_2) arterial O_2 content (mL/100 mL) = Hb (mg/dL) × 1.34 × Hb saturation (%) + 0.003 × O^2 tension (mm Hg).

$O_2ER_{i\ (\%)}$ was calculated using the following equation:[2,15]

$$O_2ER_i = VO_{2i}/DO_{2i} = (CaO_2 - CvO_2)/CaO_2$$

Metabolic Management During CPB in Group B

In group B, CI with a target of 2.4 L/min/m^2 was managed in relation to SvO_2 (the cutoff for increase in CI was <75% SvO_2, the cutoff for decrease in CI was >75% SvO_2). Related measurements were performed using a Flowmeter probe in arterial line to measure the real flow of the roller pump and the blood gas analyzer (GEM Premier 3000 IQM; Instrumentation Laboratory, Werfen Group IVD company) set to measure at 37°C[4] for
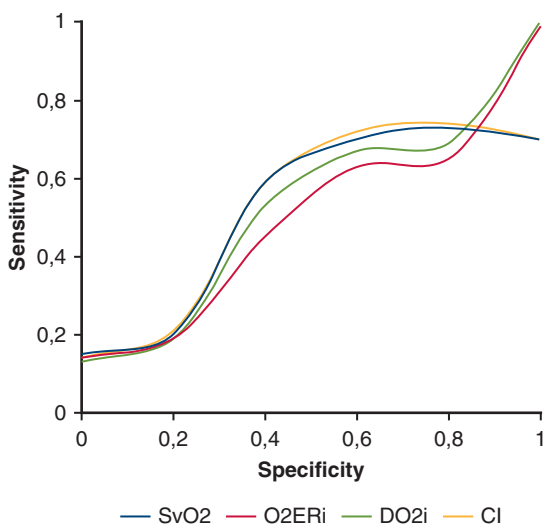

FIGURE 1. Receiver operating characteristic curves for lactate peak prediction based on target indexed oxygen delivery (DO_{2i}), indexed oxygen extraction ratio (O_2ER_i), cardiac index (*CI*), and mixed venous oxygen saturation (SvO_2).

TABLE 4. Subgroup analysis for peak blood lactate and lowest indexed oxygen delivery (DO_{2i}) in relation to indexed oxygen extraction ratio (O_2ER_i) on cardiopulmonary bypass for group A (n = 250)

Variable	No HL or HG	HL alone	HG alone	HL and HG
No. of patients	223	4	12	11
Peak blood lactate (mmol/L)	1.28 ± 0.45	3.68 ± 0.35	1.82 ± 0.65	4.91 ± 3.21
Lowest DO_{2i} (mL/min/m^2)	304 ± 21	287 ± 13	289 ± 21	195 ± 40
Highest O_2ER_i (%)	20 ± 3	25 ± 2	25 ± 3	38 ± 4

Values are presented as mean ± standard deviation. *HL*, Hyperlactatemia; *HG*, hyperglycemia; DO_{2i}, indexed oxygen delivery; O_2ER_i, indexed oxygen extraction ratio.

measurement of SvO_2 during CPB. Data were collected every 20 minutes during CPB.

CI was calculated using the following formula:

$$CI(L/min/m^2) = (Q)pump\ flow(L/min)/body\ surface\ area(m^2)$$

where pump flow (L/min) = body surface area (m^2) × CI (L/min/m^2).

SvO_2, in the clinical and intensivist practice, was a true reflection of the global balance between oxygen delivery and consumption because it is measured through the venous drainage line during CPB where venous blood returning to the right heart from the superior vena cava, inferior vena cava, and the coronary sinus have mixed. SvO_2 has been extensively studied and used clinically to monitor the global balance between DO_2 and oxygen consumption. In the literature, for patients with multiple injuries, normal SvO_2 values between 65% and 70% and increasing DO_2 are more relevant for survival.

Statistical Analysis

All data are expressed as mean ± standard error of the mean or as absolute numbers and percentage, as appropriate. Statistical analysis was performed using SPSS version 11.0 software (SPSS Inc, Chicago, Ill).
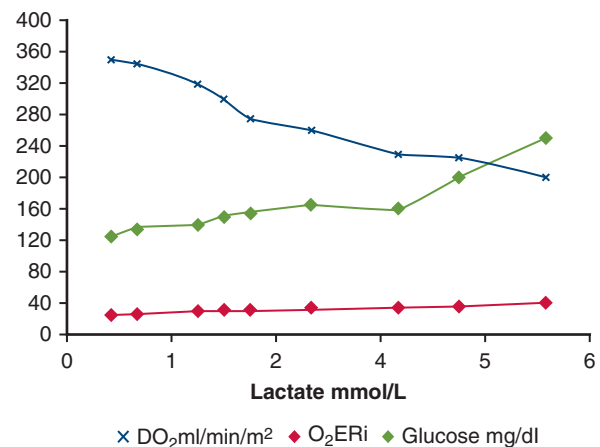

FIGURE 2. Lactate and glucose trend according to the distribution of target indexed oxygen delivery (DO_{2i}) level and indexed oxygen extraction ratio (O_2ER_i) during cardiopulmonary bypass.

TABLE 5. Subgroup analysis for peak blood lactate and lowest cardiac index (CI) in relation to mixed venous oxygen saturation (SvO$_2$) on cardiopulmonary bypass for group B (n = 250)

Variable	No HL or HG	HL alone	HG alone	HL and HG
No. of patients	187	10	21	32
Peak blood lactate (mmol/L)	1.39 ± 0.69	3.48 ± 0.38	1.79 ± 0.55	5.31 ± 3.83
Lowest CI (L/min/m^2)	2.4 ± 0.2	2.4 ± 0.1	2.4 ± 0.1	1.8 ± 0.4
Lowest SvO$_2$ (%)	80 ± 3	73 ± 1	72 ± 1	55 ± 12

Values are presented as mean ± standard deviation. *HL*, Hyperlactatemia; *HG*, hyperglycemia; *CI*, cardiac index; *SvO$_2$*, mixed venous oxygen saturation.

Univariate association with peak blood lactate was tested with a correlation matrix. Factors significantly ($P < .05$) associated with peak blood lactate at this preliminary step were entered into a stepwise forward multivariable linear regression analysis, with adequate corrections to avoid multicollinearity within the model. The multivariable approach was applied to assess the independent association between the variables tested and peak blood lactate. Subsequently, the population was explored in terms of HL (>3 mmol/L) incidence. Normally distributed continuous variables are expressed as means ± standard deviation, and categorical variables as frequencies and percentages. DO$_{2i}$ in relation to target O$_2$ER$_i$ vs CI in relation to SvO$_2$ during CPB were tested for association with peak lactate and peak glucose blood. Intraoperative variables were tested for predictive ability of HL by using a receiver operating characteristic analysis. Postoperative outcome was firstly analyzed in the population with or without HL during CPB using a univariate approach (Student *t* test for unpaired data or relative risk analysis) and was subsequently corrected for other covariates.

RESULTS

Demographic, preoperative, and operative details of the patient population are shown in Tables 1 and 2. Eight pre- and intraoperative factors were found to be significantly associated with peak blood lactate level during CPB at univariate analysis (Table 3): age, isolated coronary operation, lowest pump flow, lowest temperature, Hct, and DO$_{2i}$ were negatively correlated with peak blood lactate value during CPB, whereas CPB duration and peak blood glucose were positively correlated with peak blood lactate value during CPB. The same intraoperative factors were tested for

FIGURE 3. Lactate and glucose trend according to the distribution of cardiac index (*CI*) level and mixed venous oxygen saturation (*SvO$_2$*) during cardiopulmonary bypass.

predictivity of HL with receiver operating characteristic analysis (Figure 1). The area under the curve was significant for all factors. We therefore decided to explore the adequate cutoff values for target DO$_{2i}$ in relation to O$_2$ER$_i$ versus CI in relation to SvO$_2$ ratio during CPB as possible predictors of HL. A cutoff of DO$_{2i}$ <270 mL/min/m^2 in relation to O$_2$ER$_i$ $>35\%$ during CPB in group A (Table 4 and Figure 2) and a cutoff of CI <2.4 L/min/m^2 in relation to SvO$_2$ $<65\%$ in group B (Table 5 and Figure 3) were found to have a positive predictive value of 80% (sensitivity 73%, specificity 76%) and 75% (sensitivity 68%, specificity 67%), respectively (Figure 4). A cutoff of 155 mg/dL for peak blood on CPB showed a positive predictive value of 85% (sensitivity 84%, specificity 83%) (Table 6). A cutoff of DO$_{2i}$ >290 mL/min/m^2 in relation to O$_2$ER$_i$ 24% during CPB in group A (Figure 2) and a cutoff of CI >2.4 L/min/m^2 in relation to SvO$_2$ $>75\%$ during CPB in group B (Figure 3) were found to have a negative predictive value of 78% (sensitivity 69%, specificity 75%) and 62% (sensitivity 49%, specificity 59%), respectively (Figure 4). A cutoff of 128 mg/dL for peak blood glucose on CPB showed a negative predictive value of 74% (sensitivity 79%, specificity 80%) (Table 7). HL (>3 mmol/L) was detected in 15 (6%) patients of group A and in 42 (16.8%) patients of group B ($P = .001$); hyperglycemia (>160 mg/dL) was found in 23 (9.2%) patients of group A and in 53 (21.2%) patients of group B ($P = .001$) (Table 8). Patients without HL or hyperglycemia had significantly lower values of peak blood lactate; patients with both HL and hyperglycemia had significantly higher peak blood lactate values than patients with only HL or hyperglycemia. Only patients with associated HL and hyperglycemia had significantly lower values of DO$_{2i}$ with higher value of O$_2$ER$_i$ for group A and lower CI with low SvO$_2$ for group B on CPB. Group A patients with higher values of DO$_{2i}$ and O$_2$ER$_i$ showed a lower incidence of HL and hyperglycemia, which was 14.4% less than in group B patients for CI and SvO$_2$ target. Patients with HL during CPB had a significant increase in serum creatinine value,[13] higher rate of prolonged mechanical ventilation time and ICU stay (Table 9 and Figure 5). Patients with hyperglycemia not associated with HL were separately investigated for the outcome variables. No significant differences in terms of morbidity or mortality were detected in association with this isolated condition.
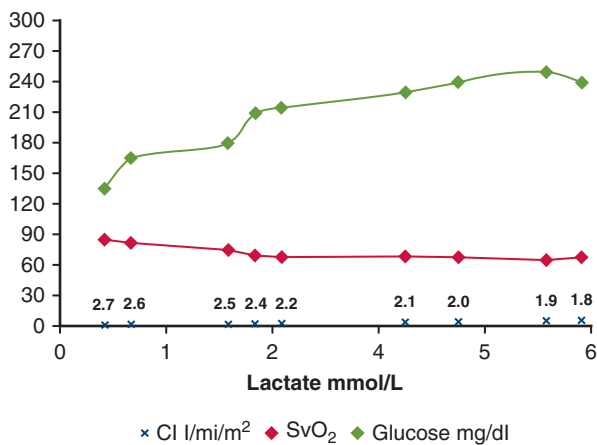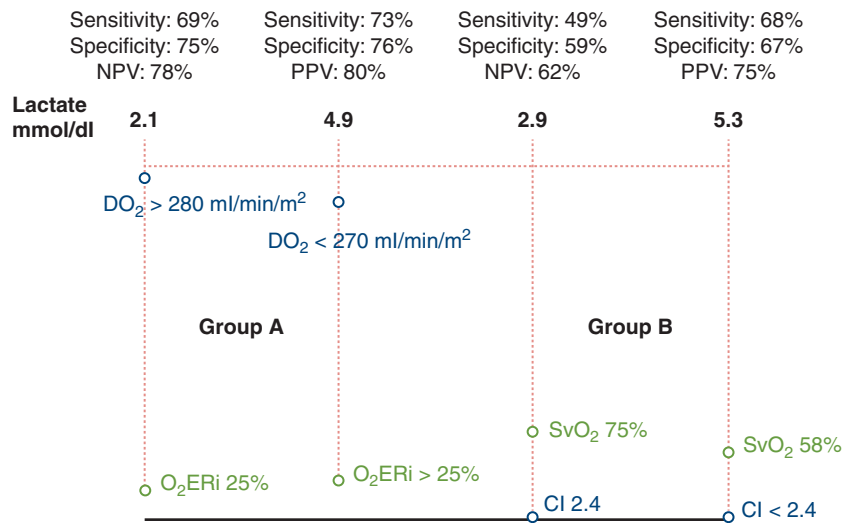
FIGURE 4. Negative predictive value (*NPV*) and positive predictive value (*PPV*) of hyperlactatemia. The receiver operating characteristic curve analysis shows that oxygen delivery (DO_2) >280 mL/min/m^2 in relation to indexed oxygen extraction ratio (O_2ER_i) 25% is more specific and sensitive than the calculated cardiac index (*CI*), and is 16 times higher as a predictive value for values <3 mmol/dL lactates. *SvO_2*, Mixed venous oxygen saturation.

DISCUSSION

In this analysis we tried to analyze the correlation of lactates and glycemia with the target managed in relation to the oxygen consumption variables, in a different way than in the previous studies, strengthening their conclusions.[1-3,9,10]

Our analysis demonstrates that the management of DO_{2i} in relation to O_2ER_i was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. The group managed with DO_2 and O_2ER_i reported a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and ICU stay, compared with group managed with CI and SvO_2.

The link between HL and hyperglycemia through the mechanism explained above was confirmed by Revelly and colleagues[16] in an elegant study dealing with cardiogenic or septic shock. The role of adrenergic agonists in this setting is well defined: in cardiogenic shock, they are both endogenous or administered for cardiovascular therapy; in our model, they are endogenous in the majority of patients. None received epinephrine during CPB, and few received norepinephrine; however, unlike epinephrine, norepinephrine usually does not increase glucose production or induce an increase in plasma lactate concentration.[6,17] The 2 mechanisms leading to HL in various clinical conditions are therefore anaerobic metabolism due to a poor DO_2 and excess lactate production due to glucose failing to enter the oxidative pathway and being degraded to lactate by the glycolytic pathway.[17] These mechanisms, if independently considered, lead to different acid–base balance conditions, the former being accompanied by metabolic acidosis and the latter not necessarily so. However, in the clinical conditions of this observational study, the acid-base balance is constantly maintained at a normal pH value by bicarbonate corrections applied by the perfusionist whenever the base excess starts decreasing. Therefore, we are unable to identify differences in HL related to different values of peak blood lactate. However, the evidence that only 4 patients demonstrated HL without hyperglycemia and that only patients with an HL-hyperglycemia syndrome had a significantly lower value of DO_2 seems to confirm that, in our specific clinical environment, HL and hyperglycemia are linked by the causative

TABLE 6. Receiver operating characteristic analysis for the 5 intraoperative positive predictive value (PPV) of hyperlactatemia

Factor	AUC	95% confidence interval	*P* value	Cutoff value	Sensitivity, %	Specificity, %	PPV, %
Lowest DO_{2i} on CPB	0.71	0.58-0.81	.001	180 mL/min/m^2	73	74	75
High O_2ER_i on CPB	0.77	0.73-0.85	.001	40%	73	76	78
Peak blood glucose on CPB	0.92	0.82-0.97	.001	160 mg/dL	81	80	85
Low CI on CPB	0.67	0.62-0.80	.009	1.8 L/min/m^2	65	69	74
Low SvO_2 on CPB	0.65	0.60-0.78	.007	55%	68	67	77

AUC, Area under the curve; *PPV*, positive predictive value; DO_{2i}, indexed oxygen delivery; *CPB*, cardiopulmonary bypass; O_2ER_i, indexed oxygen extraction ratio; *CI*, cardiac index; SvO_2, mixed venous oxygen saturation.

TABLE 7. Receiver operating characteristic analysis for the 5 intraoperative negative predictive value (NPV) of hyperlactatemia

Factor	AUC	95% confidence interval	P value	Cutoff value	Sensitivity, %	Specificity, %	NPV, %
High DO_{2i} on CPB	0.75	0.70-0.83	.001	299 mL/min/m^2	73	74	77
Low O_2ER_i on CPB	0.79	0.73-0.85	.001	24%	73	76	79
Low blood glucose on CPB	0.89	0.82-0.93	.001	128 mg/dL	79	80	74
High CI on CPB	0.68	0.65-0.79	.039	2.4 L/min/m^2	64	69	63
High SvO_2 on CPB	0.63	0.60-0.78	.035	85%	62	67	62

AUC, Area under the curve; *NPV*, negative predictive value; *DO$_{2i}$*, indexed oxygen delivery; *CPB*, cardiopulmonary bypass; *O$_2$ER$_i$*, indexed oxygen extraction ratio; *CI*, cardiac index; *SvO$_2$*, mixed venous oxygen saturation.

factor of a poor DO_2, leading on 1 hand to lactate production through the anaerobic pathway and on the other hand to a vicious cycle of lactate production due to poor ability to use glucose through the aerobic pathway.[2,5,10] Reduced oxygen content in cases of acute anemia is usually compensated by reduced blood viscosity with increased blood flow in the microcirculation and by a compensatory increase in cardiac output.[12] This last mechanism may be impaired during CPB, where pump flow is usually adjusted on the basis of the patient's body surface area and temperature, not the Hb value. On the basis of our data, the main rationale for explaining HL during CPB is a DO_2 inadequate to guarantee the needed oxygen consumption of the patient.

In the present study, we investigated the role of potentially modifiable factors related to CPB surgery in determining postoperative HL and hyperglycemia.[11] Our results demonstrate, in a relatively large series of patients treated at different sites, that a DO_{2i} <270 mL/min/m^2 with O_2ER_i >35% and low CI (<2.4 L/min/m^2) with SvO_2 <65% during CPB are associated with HL and hyperglycemia and DO_{2i} >290 mL/min/m^2 with O_2ER_i <25% and CI >2.4 L/min/m^2 with SvO_2 >75% during CPB are associated with a low incidence of HL and hyperglycemia. Various preoperative factors or comorbidities may create the right environment for HL during CPB. Age, female sex, congestive heart failure, low left ventricular ejection fraction, hypertension, atherosclerosis, diabetes, preoperative Hb value, redo or complex surgery, and emergency procedures were found to be risk factors for HL by Demers and colleagues,[1] who reported an HL incidence of 18%. Some

of these factors were confirmed in our study, and other new factors were identified; however, our study population had a significantly shorter CPB duration and a lower degree of hemodilution during CPB. Given that both these factors seem to favor the onset of HL, the lower HL rate in our population is reasonably explained. The role of CPB duration in the determination of HL during CPB has been highlighted by other authors.[1]

Some study limitations should be acknowledged. First, the design of this analysis compares 2 different extracorporeal circulation management methods. In relation to the available literature, the values taken of 75% for SvO_2 and 25% for O_2ER_i are not directly comparable because the roller pump used in group B does not correlate the calculated heart rate with the measured heart rate. Second, several patients had peripheral cannulation for CPB, which does not allow us to make a comparison between peripheral versus central cannulation. Moreover, during conventional management; we believed it appropriate not to use hypothermia because the calculated data that we were monitoring corresponded to the set objectives of 2.4 L/min flow; this nonmodification of management is intrinsically part of the retrospective nature of the study. Finally, the study focused on CPB with the use of a roller pump and does not consider the centrifuge, but it is also necessary to consider that, with its limitations, the roller pump is predominant in the daily use of cardiac surgery centers.[18] The pump flow is delivered with a roller pump, often the flow management is calculated and not measured with an ultrasonic flowmeter,[19] this often

TABLE 8. Incidence of hyperlactatemia (HL) and hyperglycemia (HG) in the study population

Variable	Group A	Group B	P value
No HL-HG	223	187	.035
HL alone	4	10	.041
HG alone	12	21	.029
HL-HG	11	32	.032
Total HG	23	53	.001
Total HL	15	42	.001

HL, Hyperlactatemia; *HG*, hyperglycemia.

TABLE 9. Hyperlactatemia (HL) during cardiopulmonary bypass and postoperative outcome

Variable	Group A (n = 250)		Group B (n = 250)	
	No HL (n = 235; 94%)	HL (n = 15; 6%)	No HL (n = 208; 83.2%)	HL (n = 42; 16.8%)
Peak serum creatinine (mg/dL)	1.1 ± 1.0	1.9 ± 1.5	1.2 ± 1.1	1.9 ± 1.5
MV time (h)	20.6 ± 45	54 ± 49	23.6 ± 55	54 ± 49
ICU stay (d)	2.8 ± 2.1	5.7 ± 4.9	3.1 ± 2.1	6.4 ± 3.9

Values are presented as mean ± standard deviation. *HL*, Hyperlactatemia; *MV*, mechanical ventilation; *ICU*, intensive care unit.
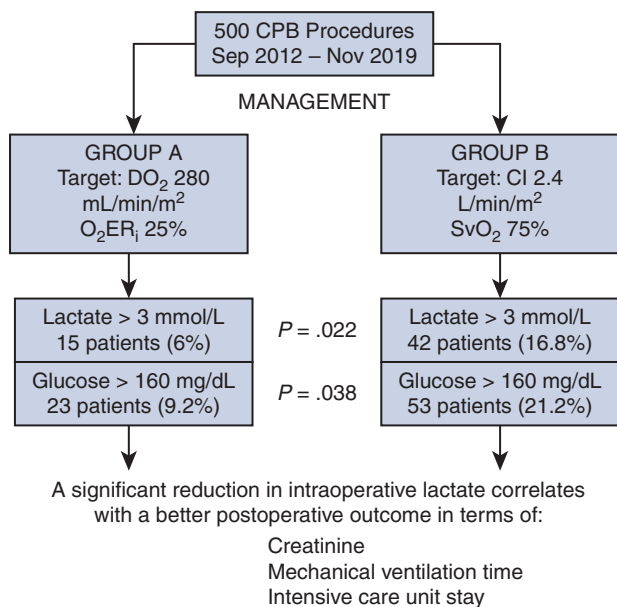
FIGURE 5. Data on 500 cardiopulmonary bypass (*CPB*) procedures were retrospectively collected, the management of indexed oxygen delivery (DO_{2i}) in relation to indexed oxygen extraction ratio (O_2ER_i) follow the CPB was more specific in terms of negative predictive value for hyperlactatemia compared with the use of cardiac index (*CI*) in relation to mixed venous oxygen saturation (*SvO₂*). That management can correlate with postoperative better outcome especially in terms of serum creatinine, mechanical ventilation time and intensive care unit stay.

involves an overestimation (eg, due to occlusion of the rotor, technique with which the occlusion is made, vacuum-assisted venous drainage use, hypothermia, viscosity, positioning of the cannula, or material of the pump). Our center used a roller pump with a half silicone tube, and an occlusion of 1 cm²/min on a three-eighths meter high column. For reasons described above, a 0.3 ± 0.2 index discrepancy occurred with ultrasound monitoring that allowed us to evaluate lower cardiac indexes that we could not have evaluated without this gap.

CONCLUSIONS

This retrospective observational study showed that management of DO_{2i} in relation to O_2ER_i was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. Group A patients showed a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and ICU stay, compared with group B patients.

Conflict of Interest Statement
The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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