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Lactate Clearance Time and Concentration Linked to Morbidity and Death in Cardiac Surgical Patients

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Background. **Early predictors of morbidity after cardiac operations are lacking. Elevated lactate concentrations in the immediate postoperative period reflect unmet metabolic demand and may be associated with outcome. This study examined the association between early plasma lactate concentrations and outcome after cardiac operations.**

Methods. **As a retrospective cohort investigation, patient information was obtained from the Cardiovascular Information and the Anesthesiology Institute's patient registries. Inclusion criteria were all adult cardiac surgical patients undergoing isolated coronary artery bypass grafting or valve procedures, or coronary artery bypass grafting with a valve procedure, from January 1, 2008, to August 7, 2008 (arterial lactate values were added to the patient registry beginning January 1, 2008).**

Results. **Lactate concentrations during the initial 12 postoperative hours of a patient's stay in the cardiovascular intensive care unit were averaged (mean lactate concentration), and linear regression concentrations over time were used to predict when the lactate concentration would reach 1.5 mmol/L in individual patients (predicted lactate clearance time). We also considered the product of the mean and clearance (product value). Predicted lactate clearance time, mean lactate concentration, and product value were associated with any type of reoperation, death, and a set of composite outcomes ($p < 0.001$ for each). The accuracy of these indices was moderate to good, with the highest C statistic (for product value) being 0.82.**

Conclusions. **Predicted lactate clearance time, mean lactate concentration, and product value are each associated with death, any type of reoperation, and a set of composite outcomes in patients undergoing coronary artery bypass grafting or valve operations, or both. Product value provided the best early prognostic guidance in individual patients.**

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Postoperative lactate concentration changes and rate of clearance to normal levels may be used to assess a patient's response to and recovery from clinical states that cause an oxygen demand–delivery imbalance. Lactic acidemia is associated with morbidity and death in critically ill patients [1–3], and postoperative lactate trends have been shown to be associated with morbidity and death in patients with septic and circulatory shock [4, 5]. Prolonged lactate clearance is also associated with increased morbidity and death in critically ill patients [6, 7]. The primary aim of this investigation was to examine the association between three arterial lactate variables—mean lactate concentration, predicted lactate clearance time, and the product of these two variables (product value)—and morbidity and death in patients undergoing coronary artery bypass grafting (CABG) or valve repair or replacement, or both.

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Material and Methods

With our Institutional Review Board's approval (IRB 5147) and waiver of the requirement for individual patient consent, patient information was obtained from the Cardiovascular Information and the Anesthesiology Institute patient registries. These registries contain demographic and clinical information on patients undergoing cardiac and noncardiac thoracic operations at our institution. Patient information is obtained through a prospective daily review of the medical history and physical assessment, anesthesia records, and clinical care notes. This information is collected at the patient's bedside in the cardiovascular intensive care unit (CVICU) after the operation. Supplemental demographic and clinical data available in other institutional databases are imported into the registry through manual and mechanized interfaces. Data validations are built into the registry to ensure data quality. Additional mechanized validations are performed quarterly to identify any quality issues that may not have been identified by the built-in validations [8, 9]. All data were collected daily by experienced

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and specially trained research personnel in a prospective manner concurrent with patient care.

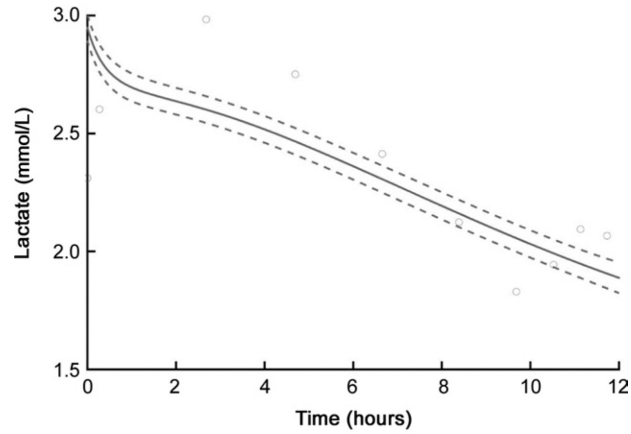
This investigation included all adult cardiac surgical patients undergoing isolated CABG, isolated valve procedures, or CABG with a valve procedure from January 1, 2008, to August 7, 2008, (arterial lactate values were added to the patient registry beginning January 1, 2008). The concentration of L-lactate in plasma was determined using amperometric measuring principles (D-lactate was not measured), with a range measurement of 0.0 to 30.0 mmol/L (reference range, 0.5 to 2.2 mmol/L).

The analysis was restricted to patients who were aged 18 years and older in whom arterial lactate concentrations were measured at least twice during the first 12 postoperative hours. We analyzed information from 1,291 consecutive adults, 295 (22.9%) of whom underwent isolated CABG (with and without cardiopulmonary bypass), 691 (53.5%) of whom underwent isolated valve procedures, and 305 (23.6%) of whom underwent combined CABG and valve procedures. We excluded 1,145 patients with no recorded lactate values and 219 patients with only one recorded lactate value. All patients were admitted to the CVICU for recovery after their operation.

Arterial lactate concentrations obtained during the first 12 postoperative hours were averaged. The mean lactate concentration is potentially useful but does not contain directional information and does not indicate whether a patient is improving or worsening. Linear regressions of lactate values during the first 12 hours were thus used to predict the time required to achieve a lactate of 1.5 mmol/L (predicted lactate clearance time). A predicted lactate clearance time of 0 hours was assigned for patients in whom a negative value was calculated (eg, the initial arterial lactate concentration was < 1.5 mmol/L). Patients with increasing lactate concentrations over time (and thus a predicted lactate clearance of infinity) were assigned a predicted time of 3 days.

A substantial majority of the patients in the study with decreasing lactate values reached normal values within 3 days or less. From histograms of these values we determined an assigned time of 3 days gave the best statistical spread of numbers without placing this subset of patients at the extreme. Our goal was to assign patients with increasing lactate concentrations a number that would distinguish them from patients with normal lactate clearance and still yield a normal statistical distribution. The average time course of lactate clearance in our patient population is shown in Figure 1A. To obtain a predictor variable that accounts for level and direction, we calculated the product of these two variables (product value).

Predicted lactate clearance time, mean lactate concentration, and the product value were examined for their association with hospital and CVICU lengths of stay, any type of reoperation, in-hospital death, and a composite set of four complications occurring during the patient's hospitalization for the index operation: death, deep sternal wound infection, permanent stroke (neurologic deficit lasting > 72 hours postoperatively), and postoperative renal failure requiring first-time



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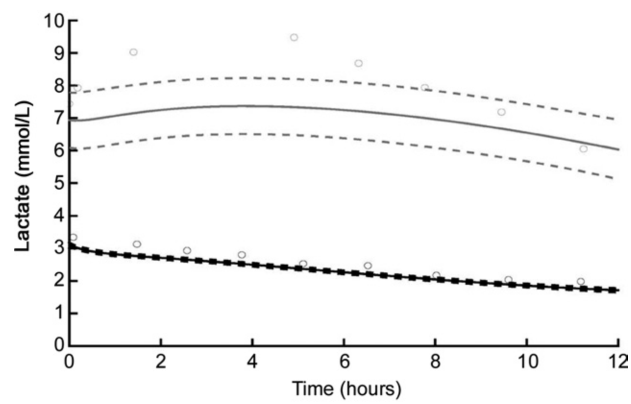

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Fig 1. (A) Average time course of lactate clearance (solid line) in our patient population during the first 12 hours after cardiac operation. Confidence intervals (dashed lines) are included. The open circles represent average lactate measurements at that interval. Lactate measures are in mmol/L and time is measured in hours. (B) Average time course of lactate clearance in survivors (black line with overlying boxes) and nonsurvivors (solid gray line). Confidence intervals (dashed lines) are included. The open circles represent average lactate measurements at that time interval.

hemodialysis. A general rule for composite outcomes is that components must be of roughly comparable severity and have similar occurrence. Any type of reoperation was thus excluded from the composite set after initial analysis revealed that the occurrence of any type of reoperation was much higher than that of the other composite measures. Reasons for any type of reoperation in our study included bleeding/tamponade, valve dysfunction, coronary graft occlusion, and other cardiac and noncardiac reasons.

Statistical Methods

Univariate analysis using Wilcoxon rank sum tests was used to assess an association for death, any type of reoperation, and composite morbidity with predicted lactate clearance time, mean lactate concentration, and product value. The correlation between the continuous variables (hospital and CVICU lengths of stay) was

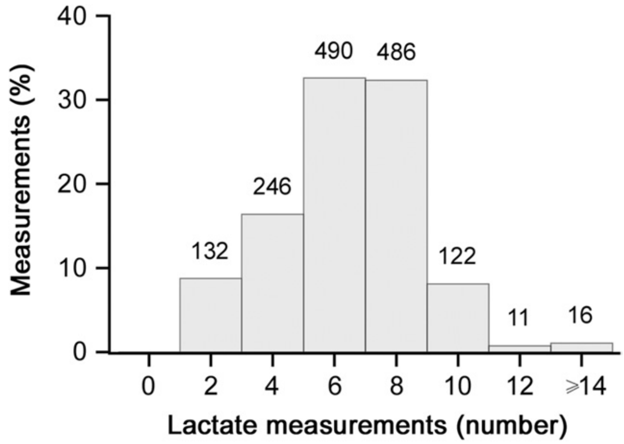

Fig 2. Frequency of plasma lactate concentration determinations during the initial 12 postoperative hours. The y axis represents the percentage of the population and the numbers above the bars represent the number of patients in each category. (total = 1,503 which is the true distribution of lactate measurements in all patients before excluding 212 patients who had missing data).

assessed using Spearman correlation coefficients. Multiple logistic regression analyses with backward variable selection procedures were used to assess the association between the predicted lactate clearance time, mean lactate concentration, product value, and binary outcomes. Log transformations were made to meet linearity assumptions.

Potential risk factors in the initial models included history of infective endocarditis, use of β-blockers within 24 hours preoperatively, use of lipid-lowering drugs within 24 hours preoperatively (and if so, whether the agent was a statin), any type of reoperation, CABG operation, valve repair or replacement, age, and elective vs urgent vs emergency operative status. Receiver operating characteristic curve analysis under logistic regression was used to evaluate the prediction accuracy of predicted lactate clearance time, mean lactate concentration, and product value for any type of reoperation, death, and the composite set of outcomes.

C statistics are reported and were used in this investigation to help determine the accuracy of the selected measures to predict the selected outcomes. The C statistic is a measure that indicates how well a prediction model or risk score discriminates between patients who do and do not have an event. In this investigation, it was used to determine how well predicted lactate clearance time, mean lactate concentration, and product value were able to discriminate between patients who died, needed any reoperation, or experienced at least one event that defined our composite outcome. C statistic values range from 0.5 to 1.0, with a value of 1.0 assigned to a prediction model or risk score with a perfect ability to discriminate between patients who do and do not have an event. We used a C statistic value exceeding 0.8 as a cutoff for good clinical utility because values of less than 0.60 have no clinical utility, values from 0.6 to 0.7 have limited clinical utility, values from 0.7 to 0.8 have moderate clinical utility, and values exceeding 0.8 are adequately able to discriminate between patients who do and do not have an event and potentially have good clinical utility [10].

Results

Figure 1A demonstrates the average lactate clearance in our patients. Figure 1B separates the lactate clearance curve in Figure 1A into two different lactate clearance curves, one for survivors and another for nonsurvivors. The number of lactate values available per patient ranged from 2 to 30 (Fig 2). The frequencies of the adverse outcomes ranged from 0.93% for deep sternal wound infection to 13.6% for any type of reoperation (Fig 3). The frequency of the composite outcome was 9.06% (with any type of reoperation excluded). A subanalysis of the types of reoperations performed at any time during the hospital stay revealed that 105 (8.13%) were performed for bleeding/tamponade, 4 (0.31%) for valve dysfunction, 1 (0.08%) for coronary graft occlusion, 38 (2.94%) for other cardiac reasons and 82 (6.35%) for other non cardiac reasons.

Predicted lactate clearance time, mean lactate concentration, and product value were reliable predictors ($p < 0.001$) of death (Table 1), any type of reoperation (Table 2), and the defined composite set of outcomes (Table 3). Multivariate analysis indicated that these measures were independent predictors. The three lactate measures were less predictive of hospital and CVICU lengths of stay, with poor correlation coefficients (range, 0.1 to 0.24; Table 4).

Predicted lactate clearance time was predictive of death (C statistic, 0.72; $p < 0.001$; Fig 4), any type of reoperation (C statistic, 0.62; $p < 0.001$), and the composite set of outcomes (C statistic, 0.70; $p < 0.001$). It was most effective at predicting death and least effective at predicting any type of reoperation. The C statistic value for predicting death was the only value greater than 0.7,

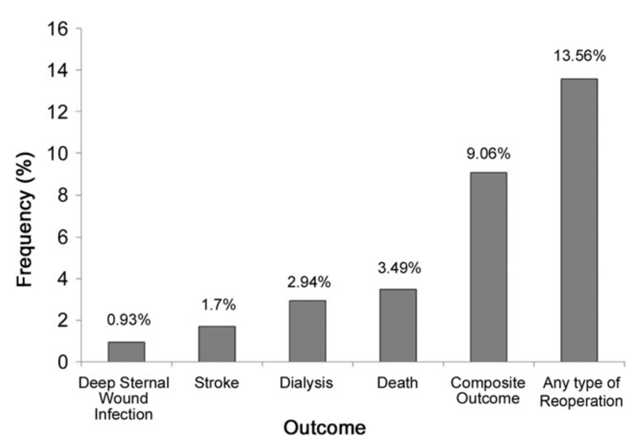

Fig 3. Frequency of adverse outcomes is shown in a sample size of 1,291 patients. Any type of reoperation was not included in the composite set after initial analysis showed its frequency was much higher than the other measured outcomes because it would influence the composite measure significantly more than the other measured outcomes. Death was defined as in-hospital death. Numbers above the bars represent the incidence of each outcome.

Table 1. Association of Lactate Indices With Complication of Death

	Death		No Death		
Variable	No.	Median (25th, 75th)	N	Median (25th, 75th)	C Statistic[a]
Predicted time (h)	45	48.0 (25.1, 48.0)	1246	12.1 (6.7, 48.0)	0.72
Mean lactate (mmol/L)	45	5.3 (2.1, 9.9)	1246	2.0 (1.4, 3.1)	0.77
Product value ($h \cdot mm \cdot L^{-1}$)	45	127 (75.8, 353)	1246	34 (12.1, 77.1)	0.82

[a] By the Wilcoxon rank sum test, corresponding values of $p < 0.001$ for all factors.

Mean lactate = mean lactate concentration; predicted time = predicted lactate clearance time; product value = product of mean lactate concentration and predicted lactate clearance time.

a conventional cutoff for determining if a variable is of moderate clinical utility.

Mean lactate concentration was predictive of death (C statistic, 0.77; $p < 0.001$; Fig 4), any type of reoperation (C statistic, 0.66; $p < 0.001$), and the composite set of outcomes (C statistic, 0.68; $p < 0.001$). Mean lactate concentration was more effective than predicted lactate clearance time at predicting death. Again, the C statistic value for predicting death was the only value greater than 0.7.

Product value was predictive of death (C statistic 0.82; $p < 0.001$; Fig 4), any type of reoperation (C statistic 0.68; $p < 0.001$), and a composite set of outcomes (C statistic 0.74; $p < 0.001$). Among the three lactate indices, product value was the most robust measure for predicting all three outcomes (ie, death, any type of reoperation, and the composite set of outcomes). The C statistic values for predicting death and the composite set of outcomes were both greater than 0.7.

Of the covariates analyzed, history of endocarditis and surgical status were independent predictors of death and composite morbidity. CABG was an independent predictor of death only, and patient age was an independent predictor of composite morbidity only.

Comment

Lactate concentrations increase in the setting of anaerobic metabolism and tissue hypoxia and in response to stimulation of β-2 adrenergic receptors [10–13]. Cardiopulmonary bypass increases plasma lactate concentration and decreases lactate clearance [14, 15].

Elevated serum lactate concentrations are associated with an increased risk of death in a variety of settings, including infection [16], trauma [17], sepsis [18], intraaortic balloon pump use [19], and operation [20–22]. Elevated plasma lactate concentrations are also associated with increased morbidity and death in pediatric cardiac surgical patients [20, 23–25]. In addition, elevated lactate concentrations in patients recovering from CABG are associated with increased morbidity and death [26].

The results of this investigation demonstrate that elevated mean plasma lactate concentrations and prolonged lactate clearance times (as well as the product of these measures) are associated with increased morbidity and death in patients undergoing CABG or valve operations, or both. Among the evaluated factors, product value was more effective (eg, had higher C statistic values) at predicting adverse outcomes than mean lactate concentration or predicted lactate clearance time. Interestingly, however, the evaluated lactate variables correlated poorly with hospital and CVICU lengths of stay (eg, low coefficients of correlation) and thus do not appear to be clinically useful for predicting length of stay.

Among the three lactate indices evaluated, product value had the highest C statistic values and thus the best combination of sensitivity and specificity for predicting death and morbidity. Mean lactate concentrations during the first 12 hours of CVICU admission had the next best predictive ability. Mean lactate concentration may nonetheless have the best clinical utility of the indices we examined because it is the easiest to obtain (eg, does not require linear regression analysis to obtain) and has only a slightly lower predictive ability than product value.

The indices used in this investigation may provide clinicians with an early indication of a patient's likelihood of experiencing major complications. The indices seem most useful in predicting death; the C statistic values for the three measures exceeded 0.7 and therefore

Table 2. Association of Lactate Indices With Complication of Any Type of Reoperation

	Reoperation		No Reoperation		
Variable	No.	Median (25th, 75th)	N	Median (25th, 75th)	C Statistic[a]
Predicted time (h)	175	30.4 (11.1, 48.0)	1116	11.7 (6.6, 48.0)	0.62
Mean lactate (mmol/L)	175	3.1 (1.7, 5.0)	1116	2.0 (1.4, 2.9)	0.66
Product value ($h \cdot mm \cdot L^{-1}$)	175	69.9 (35.2, 150)	1116	31.9 (11.7, 73.7)	0.67

[a] By the Wilcoxon rank sum test, corresponding values of p were < 0.001 for all factors.

Mean lactate = mean lactate concentration; predicted time = predicted lactate clearance time; product value = product of mean lactate concentration and predicted lactate clearance time.

Table 3. Association of Lactate Indices With Complication of Composite Morbidity[a]

	Composite Morbidity		No Composite Morbidity		
Variable	No.	Median (25th, 75th)	N	Median (25th, 75th)	C Statistic[b]
Predicted time (h)	82	48.0 (14.8, 48.0)	1209	11.9 (6.6, 48.0)	0.69
Mean lactate (mmol/L)	82	3.3 (1.8, 7.4)	1209	2.0 (1.4, 3.1)	0.68
Product value ($h \cdot mm \cdot L^{-1}$)	82	87.3 (45.9, 253)	1209	33.6 (11.9, 76.8)	0.74

[a] Included death, deep sternal wound infection, permanent stroke (neurologic deficit lasting > 72 hours postoperatively), and postoperative renal failure requiring first-time hemodialysis. [b] Wilcoxon rank sum test corresponding values of p were < 0.001 for all factors.

Mean lactate = mean lactate concentration; predicted time = predicted lactate clearance time; product value = product of mean lactate concentration and predicted lactate clearance time.

are at least of moderate clinical utility. Product value had a C statistic of 0.82 for predicting death and therefore has a moderate to good ability to discriminate between patients who will and will not survive (in hospital) after CABG or valve repair or replacement, or both. Most of the C statistic values for predicting any type of reoperation and a composite set of outcomes in our investigation were less than 0.7 and therefore of limited clinical utility.

We advocate the use of lactate variables in the clinical setting to help provide an overall clinical picture. Any specific action undertaken would be highly individualized. An increased number of serum lactate values would strengthen the reliability of the overall clinical picture provided.

Our results are consistent with reports in surgical and nonsurgical settings where elevated lactate concentrations were associated with morbidity and death [1–3, 27]. In addition, prolonged lactate clearance was shown to be associated with increased morbidity and death in critically ill patients [6, 7, 28].

In postcardiac surgical patients, the use of normal lactate concentrations as a therapeutic goal is associated with decreased morbidity and hospital length of stay [29]. Hyperlactatemia (lactate level > 2 mmol/L) has been reported to be present in 36% of cardiac surgical patients and is predictive of death [30]. In addition, a recent investigation has brought into question what the appropriate reference range for lactate values in critically ill patients should be [31]. The investigation showed that lactate concentrations within the high normal range (> 0.75 mmol/L) are independently associated with hospital death. Available results, including ours, are consistent in showing that elevated lactate concentrations or poor lactate clearance, or both, in critically ill and postsurgical patients (including after cardiac operations) are associated with morbidity and death.

Among the study's limitations are that it was observational and some patients had a small number of lactate measurements, which could have decreased the ability to obtain reliable averages and predict lactate clearance times. Furthermore, the lactate concentrations used in this investigation were obtained at variable intervals, but presumably more often when clinicians were concerned about a particular patient's condition which could have introduced bias toward worse outcomes. Since lactate levels were obtained from arterial blood gas (ABG) samples, patients with few or no postoperative ABGs had a similarly low number of lactate values (typical of patients who were weaned from ventilator support quickly and presumably had an uneventful postoperative course). Excluding these patients

Table 4. Correlation Coefficients of Lactate Indices for Length of Stay

	Correlation Coefficient[a]	
Factor	Hospital LOS	ICU LOS
Predicted time (h)	0.19	0.23
Mean lactate (mmol/L)	0.10	0.11
Product value ($h \cdot mm \cdot L^{-1}$)	0.21	0.24

[a] Values for p were < 0.001 for all factors. The Spearman correlation coefficient was used.

ICU = intensive care unit; LOS = length of stay; mean lactate = mean lactate concentration; predicted time = predicted lactate clearance time; product value = product of mean lactate concentration and predicted lactate clearance time.

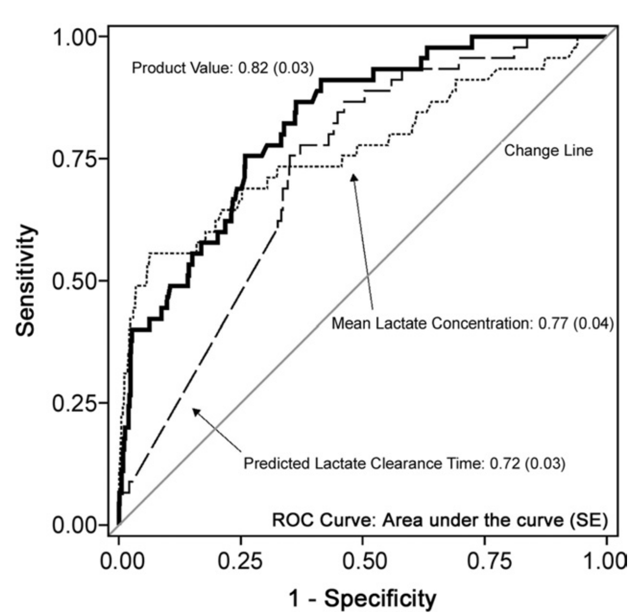

Fig 4. Combined receiver operating characteristic curve (ROC) plot is shown for predicting death from lactate clearance time (C statistic, 0.72; dashed line), from mean lactate concentration (C statistic, 0.77; dotted line), and from product value (C statistic, 0.82; bold, solid line). The standard error (SE) is shown.

(n = 1,364) likely increased the frequency of adverse outcomes. Our results are based on a "test set"; the investigation should be repeated with a validation set, perhaps from another institution.

Some patients in this investigation likely received lactated Ringer's solution during the postoperative period, which contains 28 mmol/L DL-lactate. This would have affected lactate laboratory values and was not controlled for. In addition, D lactate was not measured in this investigation, and this could have affected the results.

Because the number of patients in the cohort who died was very small, deriving reliable lactate parameters that are associated with death may not be possible.

In conclusion, predicted lactate clearance time, mean lactate concentration, and the product value (predicted lactate clearance time × mean lactate concentration) are independent predictors of death, any type of reoperation, and a set of composite outcomes in patients undergoing CABG or valve repair or replacement, or both. Among these, the product value was the most reliable predictor of postoperative death (C statistic, 0.82) and could thus serve as a general prognostic guide in individual patients during the early postoperative period. Mean lactate concentration may have better clinical utility, however, because it is less cumbersome to calculate, although the addition of ICU software would facilitate the calculation of product value. The predicted lactate clearance had only moderate power to predict death. The described lactate variables had only moderate predictive power for a set of composite outcomes and any type of reoperation, and would likely add very little to serial lactate measurements obtained from routine postoperative arterial blood gases.

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