Intensive Care Med (1991) 17:320–324

Intensive Care Medicine
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Blood lactate and mixed venous-arterial PCO_2 gradient as indices of poor peripheral perfusion following cardiopulmonary bypass surgery

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Received: 10 August 1990; accepted: 4 April 1991

Abstract. Conventional indices of tissue perfusion after surgery involving cardiopulmonary bypass (CPB) may not accurately reflect disordered cell metabolism. Venous hypercarbia leading to an increased veno-arterial difference in CO_2 tensions (V-aCO_2 gradient) has been shown to reflect critical reductions in systemic and pulmonary blood flow that occur during cardiorespiratory arrest and septic shock. We therefore measured plasma lactate levels and V-aCO_2 gradients in 10 patients (mean age 57.2 years) following CPB and compared them with conventional indices of tissue perfusion. Plasma lactate levels, cardiac index (CI) and oxygen uptake ($\dot{V}O_2$) all increased significantly ($p<0.05$ vs baseline levels) up to 3 h following surgery. Oxygen delivery ($\dot{D}O_2$) did not change. Plasma lactate levels correlated significantly with CI ($r=0.47$, $p<0.01$). V-aCO_2 fell significantly with time ($p<0.01$ vs baseline). There was an inverse relationship between V-aCO_2 and cardiac index and V-aCO_2 and lactate ($r=-0.37$, $p<0.05$; $r=-0.3$, $p<0.05$ respectively). We conclude that blood lactate, CI and $\dot{V}O_2$ increase progressively following CPB. An increase in lactate was associated with a decrease in V-aCO_2. An increase in V-aCO_2 was not therefore associated with evidence of inadequate tissue perfusion as indicated by an increased blood lactate concentration.

Key words: Blood lactate – Acid base balance – Cardiopulmonary bypass

The adequaacy of tissue perfusion during surgery requiring hypothermic cardiopulmonary bypass (CPB) is affected by multiple factors including alterations in blood volume, vascular tone, cardiac output, haematocrit and body temperature [1–3]. The time during which optimal tissue oxygenation is most desirable is during the post-surgical phase. Arterio-venous oxygen difference D(a-v)O_2; shunt fraction ($\dot{Q}s/\dot{Q}t$); and oxygen delivery ($\dot{D}O_2$), consumption ($\dot{V}O_2$) and extraction (O_2 Extr) may not be accurate indices of the adequacy of tissue perfusion [4]. Recently, the simultaneous analysis of arterial and venous acid-base status and gas tensions has been shown to be beneficial in assessing the adequacy of tissue perfusion during circulatory arrest [5, 6] and septic shock [7] when a marked disparity between arterial and venous acid-base status occurs. The development of significant venous hypercarbia is thought to reflect a critical reduction in systemic and pulmonary blood flow.

The aims of this study were therefore two-fold; firstly, to assess the adequacy of tissue perfusion in the period following surgery involving CPB by comparing haemodynamic data with plasma lactate levels and secondly, to investigate the possibility that mixed venous carbon dioxide levels might accurately reflect poor peripheral perfusion as indicated by this information.

Patients and methods

An open, prospective trial was carried out in 10 adult patients (8 male, mean age 56.1, range 30–73 years) scheduled for surgery involving cardiopulmonary bypass (Table 1). Exclusion criteria were intracardiac shunt, pulmonary vascular or parenchymal disease, metabolic disease that might have affected peripheral perfusion such as diabetes mellitus and absent peripheral pulses in the upper or lower extremities.

Study design

In all cases anaesthesia was performed by the same physicians (MA, JG) to ensure a standard approach. Following pre-oxygenation, anaesthesia was induced with intravenous fentanyl (10–15 μg/kg) and etomidate (0.2 mg/kg). Pancuronium (0.15 mg/kg) was used as the muscle relaxant and anaesthesia maintained with isoflurane (0.5–1.5%). Following induction of anaesthesia, a radial arterial cannula, a triple-lumen central venous catheter, a balloon-tipped flow-directed pulmonary artery catheter of the thermodilution type (7.5 G, Arrow Inc., Reading, Penn.) a urinary catheter and a pharyngeal thermometer were inserted in all patients. Oxygen and air (FiO_2 0.6) were administered to the patient via a Brompton positive-pressure ventilator (Blease Ltd., Chesham, UK). The minute volume of fresh gas flow was adjusted to maintain the arterial carbon dioxide tension ($PaCO_2$ between 4.8 and 5.5 kPa. Fluid replacement was with hetastarch (Hespan, Dupont Pharmacueticals (UK) Ltd., Stevenage, UK) and blood. Postoperatively the patients were transferred to the intensive care unit where positive pressure ventilation was continued. Patients were administered bolus intravenous doses of

Table 1. Showing patient demographic data, perfusion data and mean (±SE) baseline haemodynamic values

Patient no.	Sex	Age	Operation	CPB duration mins	Temp. °C	Flow l/min/m^2 during hypothermia	Mean perfusion pressure (mmHg)
1	M	53	ARR	103	23.4	2.14	50
2	F	73	CAVG	70	28.2	1.78	50
3	M	61	CAVG	106	26	1.73	55
4	M	59	CAVG	113	27	1.98	60
5	F	59	MVR	51	27.7	1.63	57
6	M	30	AVR	97	30	1.79	57
7	M	59	CAVG	71	26.4	1.83	60
8	M	60	CAVG	71	30.7	1.92	60
9	M	56	CAVG	90	28	1.88	60
10	M	51	CAVG	92	28	1.60	65

CI (l/min/m^2)	Lactate (mMol/l)	Hb (g/dl)	SVR (dm^2/s^5)	$\dot{D}O_2$ (ml/min/m^2)	$\dot{V}O_2$ (ml/min/m^2)	V-a CO_2 (kPa)
2.29 (0.15)	1.06 (0.11)	11.9 (0.40)	1374 (156)	372 (21)	74 (4.1)	1.2 (0.1)

BSA body surface area, CPB cardio-pulmonary bypass, AAR aortic root replacement, AVR aortic valve replacement, MVR mitral valve replacement, CAVG coronary artery vein grafts. $\dot{V}O_2$ oxygen consumption, $\dot{D}O_2$ oxygen delivery, SVR systemic vascular resistance, Hb haemoglobin conc., V-a CO_2 mixed venous-arterial CO_2 gradient

papaveretum (1–2.5 mg) and midazolam (1–2.5 mg) as required to treat pain and distress. Patients were weaned from the ventilator and extubated when assessed to be appropriate by the clinical staff according to normal clinical practice.

Cardiopulmonary bypass

During bypass, oxygenation and anaesthesia were maintained using a bubble oxygenator (William Harvey H-1700, Bard, Crawley, U.K.) with a isoflurane vaporiser in the gas inlet circuit to maintain anaesthesia. A flow of between 1.6 and 2.2 l/min/m^2 was maintained according to the individual surgeons preference. Mean perfusion pressure during CPB was maintained between 50 and 60 mmHg using isoflurane to vasodilate and metaraminol to vasoconstrict when required. Moderate hypothermia (28 °C) was used during bypass, but all patients were re-warmed to 37 °C before it was discontinued.

Experimental protocol

Blood samples were taken and haemodynamic measurements made as follows: baseline (after induction of anaesthesia); immediate pre-bypass; immediate post-bypass; 30 min after arrival in the intensive care unit (ICU) and 30, 60, 120, and 180 min later. A final set of measurements and samples were taken 18 h after arrival on the ICU. Blood samples were taken simultaneously and anaerobically at 37 °C by the same 2 investigators from the distal lumen of the pulmonary artery catheter and the radial artery cannula.

Analytical procedures and calculations

The pH, arterial oxygen tension (PaO_2), $PaCO_2$, bicarbonate, arterial (SaO_2) and mixed venous oxygen saturations ($S\bar{v}O_2$ and haemoglobin were measured in duplicate immediately after sampling, using a Corning 176 blood gas analyser and Corning 2500 co-oximeter respectively (Corning UK Ltd, Essex, UK). Venous blood (5 ml) was removed simultaneously for the measurement of lactate levels and was immediately centrifuged, the plasma separated and frozen at −80 °C. Analysis was carried out at a later date with an enzymatic technique using lactate oxidase with amperometric detection of oxygen consumption (Analox LM3 analyser, London, UK).

Immediately after the blood samples were withdrawn, measurements were made of the following haemodynamic data; heart rate (HR); blood pressure (BP); mean blood pressure (MAP); central venous pressure (CVP); mean pulmonary artery pressure (Ppa); pulmonary artery occlusion pressure (PAOP) and cardiac output (CO), CO was measured by thermodilution in triplicate). From the measured data, oxygen content of arterial and mixed venous blood were calculated to permit the estimation of $\dot{V}O_2$, $\dot{D}O_2$ and O_2 Extr, systemic and pulmonary vascular resistances (SVR, PVR) and cardiac index (CI) using standard formulae.

Statistical analysis

Data are shown in the text as mean ±SEM. Changes in data over time were assessed using analysis of variance and statistical significance measured using Student's *t* test for paired data and the Bonferroni modification for multiple comparisons. Any statistical evidence of a significant association between haemodynamic data (CI, $\dot{V}O_2$, $\dot{D}O_2$) and arteriovenous differences in CO_2 or blood lactate were sought using regression analysis. Statistical significance was assumed at $p \leq 0.05$.

Results

The details of individual patients and perfusion data are shown in Table 1, together with the baseline values of the measured variables. The mean flow, during CPB was 1.8 l/min/m^2 (range 1.6–2.1 l/min/m^2) with a mean temperature of 27.5 °C (range 23.4–30.7 °C). Mean perfusion pressure was 57.4 mmHg (range 50–65 mmHg) and the mean duration of CPB ws 86.4 min (range 51–113 mins.).

Cardiac index increased progressively following bypass ($p < 0.05$ compared with baseline), reaching a mean maximal level of 3.1 ± 0.22 l/min/m^2 60 min after arrival in the ICU (equivalent to a 44% increase). At 18 h after the procedure it was still above baseline levels ($p < 0.05$) (Fig. 1). SVR did not fall significantly for the group as a whole during the study period, although the trend was downward. Haemoglobin fell significantly from a baseline value of 11.9 g/dl to a mean value of 9.1 g/dl post CPB ($p < 0.01$). Thereafter haemoglobin concentration increased with a mean value of 9.9 g/dl being recorded 18 h post-operatively ($p < 0.02$ compared to baseline). There was a progressive rise in plasma lactate levels from

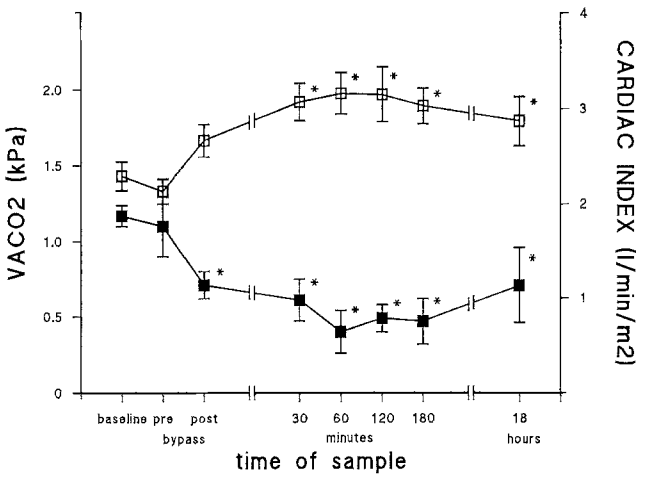

Fig. 1. Showing changes in cardiac index □ (l/min) and V-aCO$_2$ ■ (kPa) gradient with time. Values shown are means ±SEM. * signifies value significantly different from baseline ($p<0.05$)

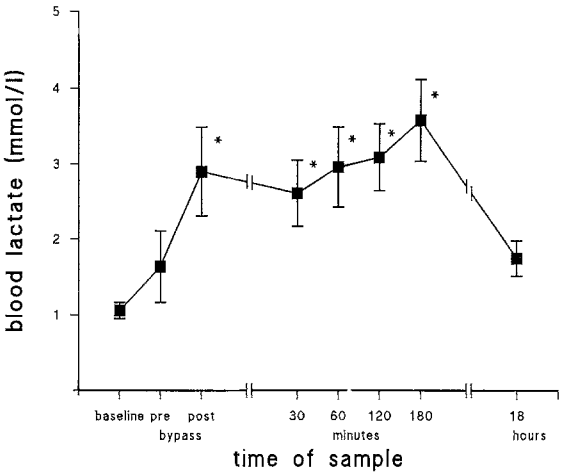

Fig. 2. Showing changes in plasma lactate (mmol/l) with time. Values shown are means ±SEM. * signifies value significantly different from baseline ($p<0.05$)

a mean baseline level of 1.1±0.11 mmol/l (normal range in our laboratory 0.63–2.44 mmol/l, $p<0.05$ compared with baseline from the first postbypass measurement) to a maximal mean level of 3.6±0.54 mmol/l 3 h post-operatively (Fig. 2). Lactate level after 18 h was 1.8±0.23 mmol/l which was not significantly different from baseline value.

$\dot{D}O_2$ did not change significantly during the study period, but $\dot{V}O_2$ increased progressively following bypass from a baseline value of 74±4.1 ml/min/m^2 ($p<0.05$ after 30 min in the ICU) reaching a maximal level of 143±15.4 ml/min/m^2 above baseline 2 h after the patients arrived in the ICU (Fig. 3). Oxygen extraction consequently increased from a mean of 20±1.4% at induction of anaesthesia to a maximal level of 38±3.0% 3 h after arrival in the ICU (Table 2). There was a positive correlation between plasma lactate levels and measurements of CI taken on the day of the operation ($r = 0.47$, $p<0.01$). There was a significant relationship between lactate and $\dot{D}O_2$ on the day of the operation ($r = 0.32$, $p<0.01$).

Arteriovenous differences in CO_2 tension fell from a baseline level of 1.2±0.07 kPa to 0.7±0.09 kPa ($p<0.01$) immediately following bypass and continued to fall to a minimal level of 0.40±0.14 kPa ($p<0.01$) 60 min after arrival on the ICU (Table 2, Fig. 1). D(a-v)O$_2$ increased progressively post-operatively, due to the fall in S$\bar{v}$O$_2$

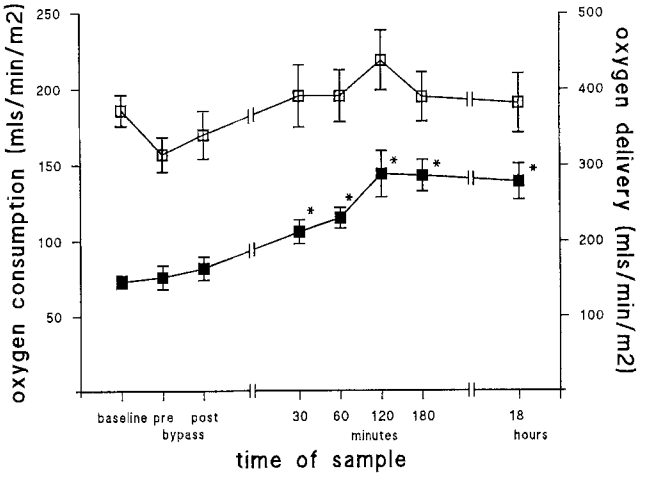

Fig. 3. Showing changes in oxygen delivery ■ (ml/min/m^2) and oxygen consumption □ (ml/min/m^2. * signifies value significantly different from baseline ($p<0.05$)

and reflecting the increased oxygen extraction (Table 2). There was no correlation between D(a-v)O$_2$ and V-aCO$_2$. There was a negative correlation between the change in V-aCO$_2$ and both CO ($r = -0.37$, $p<0.01$) and lactate ($r = -0.30$, $p<0.05$) made on the day of operation.

Table 2. Showing the changes in mean [±SE) arterial and mixed venous saturation (SaO$_2$, S$\bar{v}$O$_2$), arterial venous oxygen content difference (D(a-v)O$_2$) extraction ratio (O$_2$Extr) and mixed venous arterial CO$_2$ tension gradient (V-aCO$_2$)

	SaO$_2$	S$\bar{v}$O$_2$	D(a-v)O$_2$ (ml/l)	O$_2$Extr (%)	v-aCO$_2$ (kPa)
Baseline	0.99 (0.00)	0.82 (0.01)	33.1 (2.7)	20.1 (1.4)	1.2 (0.1)
Pre CPB	0.99 (0.00)	0.78 (0.02)	35.5 (2.1)	24.2 (1.8)	1.1 (0.2)
Post CPB	0.98 (0.00)	0.77 (0.05)	30.9 (2.6)	25.7 (3.5)	0.7 (0.1)
ICU + 30 min	0.98 (0.01)	0.71 (0.03)	35.4 (3.2)	28.9 (3.0)	0.6 (0.1)
ICU + 60 min	0.98 (0.01)	0.69 (0.03)	39.7 (2.5)	30.3 (2.4)	0.4 (0.1)
ICU + 120 min	0.98 (0.00)	0.65 (0.03)	44.7 (3.1)	33.9 (3.0)	0.5 (0.1)
ICU + 180 min	0.97 (0.01)	0.60 (0.04)	47.9 (3.1)	37.7 (3.0)	0.5 (0.1)
ICU + 18 Hr	0.98 (0.01)	0.63 (0.03)	49.9 (4.1)	37.6 (2.7)	0.7 (0.3)

Discussion

Previous studies have demonstrated a metabolic acidosis during CPB through peripheral hypoperfusion [1, 8, 9]. If plasma lactate levels are considered to be an accurate index of the adequacy of tissue perfusion, we have shown that these changes persist well into the post-operative phase such that the highest plasma lactate levels were recorded 3 h post-operatively. These findings are similar to those of other workers studying patients after both cardiac [9] and major abdominal surgery [10]. We observed a progressive rise in plasma lactate concentrations above normal levels during the post-operative period and a parallel rise in CI and $\dot{V}O_2$. The progressive increases in both CI and $\dot{V}O_2$ post-operatively can be explained, at least partially, by the effects of increasing metabolic rate through spontaneous rewarming, emergence from anaesthesia and spontaneous recovery of myocardial function. However, the apparent positive correlation between CI and lactate is rather surprising if it is accepted that an increase in plasma lactate reflects the onset of anaerobic metabolism secondary to inadequate cellular oxygen uptake. There are a number of possible explanations for this observation. Firstly, a hypermetabolic response after cardiac surgery has been described [11], which may increase oxygen demand over and above what appears to be an adequate $\dot{D}O_2$. Furthermore, an increase in oxygen extraction ratio in these circumstances may also reflect the inability of the myocardium to respond rapidly to the increased demands of the immediate post-operative period. Certainly the elevation of plasma lactate after 3 h, when the hypermetabolic response appears to be maximal [11], implies that inadequate $\dot{D}O_2$ relative to oxygen demand occured. Secondly, a fall in $\dot{D}O_2$ could result in a rise in lactate in parallel with a rise in CI provided that haemoglobin fell sufficiently. In the current study, the post-bypass increase in CI was offset almost exactly by a reduction in haemoglobin such that $\dot{D}O_2$ did not change significantly. Thirdly, a delay in the tissue washout of lactate, such that plasma levels increased only after rewarming with a consequent increase in tissue perfusion could have occurred. Fourthly, systemic microvascular control may become disordered in CPB, resulting in peripheral arteriovenous shunting and a rise in tissue lactate levels despite an apparently adequate cardiac output. Impaired cellular utilisation of oxygen due to similar mechanisms has been proposed to occur after major abdominal surgery [10]. Finally, the elevation in lactate could be due to impaired clearance. An increased plasma lactate may be a reflection of reduced hepatic clearance rather than increased lactate production [12], a mechanism that cannot be excluded in these patients. However, no evidence of impaired liver function was detected in any of our patients.

Changes in V-aCO_2 gradients have recently been described following cardiorespiratory arrest [5, 6] and septic shock [7]. If CO_2 production ($\dot{V}CO_2$) remains constant, a reduction in systemic flow will result in an increase in the V-aCO_2 gradient as predicted from the Fick relationship. With critical reductions in systemic and pulmonary blood flow venous hypercarbia and arterial hypocarbia cause a marked widening of the VaCO_2 gradient. Low pulmonary blood flow increases the ventilation: perfusion ratio of the lung causing a arterial respiratory alkalosis. Reduced pulmonary CO_2 excretion results in a venous respiratory acidosis, which more accurately reflects tissue acid-base status than the arterial respiratory alkalosis [5]. At critically low levels of peripheral perfusion the efficacy of CO_2 exchange may be impaired, further increasing venous CO_2 [13]. During anaerobic metabolism CO_2 is produced both from the buffering of acids such as lactic acid by bicarbonate and from anaerobic decarboxylation. The consequent reduction in buffering capacity of the blood results in a decrease in the relative amount of CO_2 transported as bicarbonate causing a widening of the V-aCO_2 gradient. In our patients the V-aCO_2 decreased post-operatively, showing a negative correlation with CI. There was also a negative correlation between changes in lactate and V-aCO_2. If the increased plasma lactate which occured in this study reflected inadequate peripheral perfusion, a positive correlation with V-aCO_2 might have been expected. However, CO_2 production is influenced by the change in metabolic rate that follows CPB, making V-aCO_2 gradient difficult to interpret in these circumstances. Furthermore, CO_2 is produced during the metabolism of lactate and a washout effect could further increase $\dot{V}CO_2$ as perfusion increases. Secondly, if inadequate tissue oxygen delivery occurs due to arterio-venous shunting then a fall in V-aCO_2 gradient could be associated with an increase in plasma lactate. Thirdly, all the patients studied were of low risk with good left ventricular function and did not require inotropes post-operatively. It may have been therefore that perfusion was not low enough to cause venous hypercarbia sufficiently marked to widen the V-aCO_2 gradient (even though there was a significant increase in lactate). If the study ws repeated in higher risk patients the results might be different.

There was no correlation between D(a-v)O_2 and V-aCO_2. D(a-v)O_2 increased progressively following bypass because $\dot{V}O_2$ increased with no change in $\dot{D}O_2$ (the increase in cardiac index being offset by a reduction in haemoglobin and therefore oxygen carrying capacity). The carriage of CO_2 is less dependent upon haemoglobin, which may explain the lack of correlation between D(a-v)O_2 and V-aCO_2. Thus, as D(a-v)O_2 increased V-aCO_2 fell due to the increase in cardiac output. Any comparison between these parameters in further complicated by the different units involved (V-aCO_2 is a gradient of partial pressure and D(a-v)O_2 is a gradient of content). Thus, the CO_2 content at a particular partial pressure depends on a number of factors including haematocrit, oxygen saturation and temperature [14].

We have shown that CI, plasma lactate levels and $\dot{V}O_2$ increase post-operatively after cardiac surgery, changes that are maintained well into the post-operative phase. The increase in plasma lactate may reflect persistently inadequate tissue oxygen delivery. In the patients studied V-aCO_2 gradient did not appear to reflect the adequacy of peripheral perfusion (as indicated by lactate). This study should be repeated in higher risk patients when tissue perfusion may be further impaired and an in-

crease in V-aCO_2 gradient may then predict inadequate peripheral perfusion.

References

1. Clowes GH, Neville MW, Sahaga G, Shibota Y (1958) The relationship of oxygen consumption, perfusion rate and temperature to the acidosis associated with cardiopulmonary circulatory bypass. Surgery 44:220–239
2. Moores WY (1982) Oxygen delivery during cardiopulmonary bypass. In: Utley JR (ed) Pathophysiology of cardiopulmonary bypass. Williams and Wilkins, Baltimore, pp 1–11
3. Tobias MA (1986) Choice of priming fluids. In: Taylor KM (ed) Cardiopulmonary bypass: Principles and management. Chapman and Hall, London, pp 221–248
4. Astiz ME, Rackow EC, Kaufmann B, Falk JL, Weil MH (1988) Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. Crit Care Med 16:655–658
5. Weil MH, Rackow EC, Trevino R, Grunder W, Falk JL (1986) Difference in acid base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315:153–156
6. Adrogue HK, Rashad MN, Gorin AB, Yacoub J, Madias NE (1989) Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. N Engl J Med 320:1312–1316
7. Mecher CE, Rackow EC, Astiz ME, Weil MH (1990) Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med 18:585–589
8. Shepard RB, Kirklin JW (1969) Relationship of pulsatile flow to oxygen consumption and other variables during cardiopulmonary bypass. J Thorac Cardiovasc Surg 58:694–702
9. Fiaccadori E, Vezzani A, Coffrini E, Guariglia A, Ronda N, Tortorella G, Vitali P, Pincolini S, Beghi C, Fesani F, Borghette A (1989) Cell metabolism in patients undergoing major valvular heart surgery: Relationship with intra and post-operative hemodynamics, oxygen transport, and oxygen utilization patterns. Crit Care Med 17:1286–1292
10. Waxman K, Lorene S, Nolan RN, Shoemaker W (1982) Sequential perioperative lactate determination: physiological and clinical implications. Crit Care Med 10:96–99
11. Chiara O, Giomarelli PP, Biagioli B, Rossi R, Gattinoni L (1987) Hypermetabolic response after hypothermic cardiopulmonary bypass. Crit Care Med 15:995–1000
12. Narins RG, Krishna CG, Bressler L (1987) The metabolic acidoses. In: Maxwell MH, Kleeman CR, Narins RG (eds) Clinical Disorders of Fluid and Electrolyte Metabolism. McGraw-Hill, New York, pp 597–642
13. Randal H, Cohen J (1966) Anaerobic CO_2 production by the dog kidney. Am J Physiol 211:493–505
14. Kelman GR (1967) Digital computer procedure for the conversion of PCO_2 into blood CO_2 content. Respir Physiol 3:111–113

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