The Association Among Gastric Mucosal pH, Endotoxemia, and Low Systemic Vascular Resistance After Cardiopulmonary Bypass

Paul Myles, MB BS, MPH, DipRACOG, DA(UK), FFARCS(Irel), FANZCA, Mark Buckland, MB BS, FANZCA, Graham Cannon, MB BS, FANZCA, Michael Bujor, MB BS, FANZCA, James Anderson, MSc, CCP, Bob Salamonsen, MB BS, MD, FANZCA, and Bruce Davis, MB BS, FRACS

Objective: **Previously, it was found that a number of patients suffer a "low systemic vascular resistance syndrome" after cardiopulmonary bypass, and this was hypothesized to be secondary to endotoxemia, resulting from intestinal ischemia during bypass.**

Design: **Prospective cohort.**

Setting: **University teaching hospital.**

Participants: **Thirty-two patients undergoing cardiac surgery.**

Interventions: **A number of variables relating to adequacy of tissue perfusion were measured at seven time periods perioperatively: cardiac output, systemic vascular resistance, oxygen delivery and consumption, oxygen extraction ratio, gastric mucosal pH, serum lactate, and endotoxin levels.**

Measurements and Main Results: **Investigators could not find any association between systemic vascular resistance and mucosal pH or endotoxin levels after bypass. There were significant changes in oxygen flux and extraction ratio ($p < 0.001$) as well as serum lactate ($p < 0.001$). There was no significant change in endotoxin levels or mucosal pH. The systemic vascular resistance at 6 hours postbypass could be predicted from the vascular resistance reading at 1 hour postbypass by a regression equation. A significant correlation between systemic vascular resistance and mixed venous oxygen was found at 4 and 6 hours postbypass ($p < 0.01$) as well as with oxygen extraction ($p < 0.01$). There was a negative correlation between mucosal pH and serum lactate, particularly at 6 hours postbypass ($p < 0.01$). There was no correlation between mucosal pH and endotoxin levels, oxygen flux, or cardiac output.**

Conclusions: **The investigators therefore could not find any evidence that intestinal ischemia during bypass, as measured by gastric mucosal pH, predisposes to endotoxemia, or low systemic vascular resistance after cardiac surgery.**

KEY WORDS: anesthesia, cardiac surgery, cardiopulmonary bypass, endotoxins, gastric tonometry, systemic vascular resistance

THE LOW SYSTEMIC vascular resistance (SVR) syndrome after cardiac surgery and cardiopulmonary bypass (CPB) remains a poorly understood phenomenon, despite its common occurrence.[1,2] Septic shock and the low SVR syndrome share many features: high cardiac output, low SVR, peripheral shunting of blood flow, and tissue acidosis. It has also been demonstrated that the hemodynamic features of septic shock are caused by release of endotoxins.[3-5] This has also been shown to occur during cardiac surgery, after release of the aortic cross-clamp.[6-10]

It has been suggested that post-CPB endotoxemia is caused by intestinal ischemia during aortic cross-clamping, with leakage of endotoxin through the bowel wall.[6,7,9-14] Intestinal ischemia continues to occur to a lesser degree for at least 8 hours after cardiac surgery and therefore parallels the pattern of the low SVR syndrome. It was the study's hypothesis that the low SVR syndrome is secondary to endotoxemia, resulting from intestinal ischemia during CPB.

MATERIALS AND METHODS

Patients scheduled for elective cardiac surgery were enrolled in this open study after Institutional Ethics Committee approval and written, informed consent. Patients were excluded if they had any evidence of sepsis (temp >37°C, WBC [white blood cell count] >12,000/mL), had a history of esophageal varices or inflammatory bowel disease, or were taking corticosteroid medication.

All patients received a standardized general anesthetic. They were premedicated with oral temazepam, 10 to 20 mg, IM papaveratum, 10 to 20 mg, and hyoscine, 0.2 to 0.4 mg; induced with IV diazepam, 5 to 10 mg, fentanyl, 500 to 1,500 μg, and pancuronium, 8 to 12 mg; and, anesthesia was maintained with increments of enflurane (0.2% to 1.5%) and fentanyl, 500 to 1,500 μg. Perfusion during CPB was also standardized, using a hollow-fiber capillary membrane oxygenator (Capiox E; Terumo, Tokyo, Japan) and arterial line filter (32 micron), with moderate hypothermia (27 to 32°C), and alpha-stat pH management; nonpulsatile flow rates were initially set at 2.4 L/min/m^2 at 37°C and 1.8 L/min/m^2 at 25°C, maintaining a mean perfusion pressure of 50 to 70 mmHg. Mixed venous oximetry (SvO_2) monitoring was also used, and flows adjusted to maintain SvO_2 above 70%.

Before induction of anesthesia, a peripheral intravenous catheter, radial arterial catheter, and pulmonary artery catheter were inserted using local anesthetic. After induction, a gastric tonometry catheter (TON20024816; Tonometrics, Worcester, MA) was inserted, with its position confirmed by auscultation; this was later verified by x-ray on return to the intensive care unit (ICU). The tonometer balloon was then filled with 2.5 mL of saline after elimination of air bubbles.

Patients were managed according to standard protocols, with initial ventilator management consisting of an inspired oxygen concentration of 70%, tidal volume of 10 mL/kg, and a respiratory rate of 10 to 12 breaths per minute.

From the Alfred Hospital, Melbourne, Australia.

Funded in part by the Alfred Hospital Whole Time Medical Specialist's Private Practice Fund.

1053-0770/96/1002-0005$3.00/0

Patients were weaned from mechanical ventilation as soon as they responded to verbal stimuli, rewarming was complete, hemodynamic stability had been established, and blood loss was satisfactory (less than 100 mL/hr).

Hemodynamic measurements were taken at the following time intervals:

Time period 1: pre-induction
Time period 2: 30 minutes postinduction
Time period 3: 15 minutes after commencing CPB
Time period 4: 15 minutes post-CPB
Time period 5: 1 hour post-CPB
Time period 6: 4 hours post-CPB
Time period 7: 6 hours post-CPB

Hemodynamic measurements consisted of central venous pressure, pulmonary artery wedge pressure, mean arterial blood pressure, cardiac output (CO), and systemic vascular resistance (SVR). Blood temperature was recorded from the thermistor of the pulmonary artery catheter, except during CPB where nasopharyngeal temperature was used. Cardiac output was measured using the thermodilution technique. All readings were performed at end-expiration, in triplicate, with each reading accepted if within 10% of each other. The average reading was then used. SVR was calculated from the Hewlett Packard Component Monitoring System.

At the previously mentioned time periods, blood samples were also collected for mixed venous oxygen saturation (measured by co-oximeter), arterial blood gases, lactate levels, and hemoglobin concentration. At time periods 3 to 6, 5 mL of blood were also collected for endotoxin levels. Other data collected included aortic cross-clamp time, use of epinephrine, dopamine, and nitroglycerin (NTG), and urine output during the operative procedure and for the 6-hour time period after cross-clamp release.

Oxygen delivery (DO_2) and consumption (VO_2) were calculated from standard formulae, using a value of 1.34 mL/g for hemoglobin-bound oxygen, and 0.003 mL/100 mL/mmHg for dissolved oxygen. Oxygen extraction ratio (ER) was then calculated as the ratio of VO_2/DO_2.

A chromogenic limulus amebocyte lysate assay (Whittaker Bioproducts, MA) was used to measure endotoxin. A meticulous aseptic collection technique was used, with employment of a trained microbiologist for the endotoxin assay. Five-mL blood samples were collected into pyrogen-free tubes, then stored at −70°C until the end of the trial period, for batch testing. After dilution in pyrogen-free water and heat inactivation at 70°C for 10 minutes, calibration curves of absorbence versus concentration were constructed. Results are expressed as endotoxin units (EU) per mL (where 1000 EU/mL is approximately 100 ng/mL). The endotoxin levels were corrected for hemodilution, using the baseline/post-CPB hematocrit ratio.

After sufficient time for equilibration of carbon dioxide (CO_2) between the saline and the gastric lumen, anaerobic samples of the tonometer saline and arterial blood were taken and analyzed with standard pH and blood-gas measurements. Gastric mucosal pH (pHi) was calculated by a modification of the Henderson-Hasselbach equation (Tonometrics, Worcester, MA):

$$pHi = 6.1 + [\text{arterial } HCO_3/F \times \text{tonometer saline } PCO_2]$$

where F = time-dependent factor for equilibrated samples.

All data were recorded on a data sheet, then stored on a computer file (SPSS V4.0 Data Entry). Repeated measures analysis of variance (ANOVA) was used to analyze the changes in SVR, DO_2, VO_2, serum lactate, endotoxin levels, and pHi. Univariate Pearson's correlation coefficients were first calculated to describe the association between SVR and the following variables: preceding SVR reading, CO, SvO_2, DO_2, VO_2, serum lactate, endotoxin levels, pHi, aortic cross-clamp time, and urine volume. Multiple stepwise linear regression analysis was then used to predict SVR at 6 hours post-CPB from significant correlates, after adjusting for hemoglobin concentration and temperature. All statistical analyses were performed with SPSS/PC+ V4.0 software. To account for multiple comparisons, a p value of less than 0.01 was considered significant.

RESULTS

A total of 32 patients were studied, 31 had undergone CABG, and 1 patient had a combined CABG and valve replacement. All were treated with an NTG infusion, and 4 required an epinephrine infusion after CPB. There were no operative deaths. Their demographic details and perioperative characteristics are presented in Table 1. The average time to extubation was 10 hours after ICU admission.

Their hemodynamic changes are shown in Fig 1 and Table 2. The sequential changes in serum lactate, endotoxin levels, and pHi are shown in Fig 2. There was a significant increase in the serum lactate over time ($p < 0.001$), but no significant changes in endotoxin levels and pHi ($p = 0.63$ and $p = 0.39$, respectively). Although there was no change in the mean endotoxin level, there was an increase in the variability, with a range of 204 to 2529 EU/mL at 6 hours post-CPB. The changes in DO_2 and VO_2 are shown in Fig 3. The oxygen ER mean (SD) for the corresponding time periods were 0.21(0.05), 0.22(0.06), 0.22(0.06), 0.26(0.08), 0.29(0.06), 0.36(0.09), and 0.38(0.09). There were signifi-

Table 1. Demographic Details and Perioperative Characteristics

	Mean (SD) or Proportion	Range
Age (years)	62 8 (9 0)	44-79
Male/female	24/8	——
Preop hemoglobin (mg/dL)	13.8 (1.7)	9 9-16 3
Preop mean BP (mmHg)	88 (15)	53-108
Aortic cross-clamp time (mins)	61 4 (21)	32-128
Epinephrine used post-CPB	4/32	——
Dopamine used post-CPB	1/32	——
NTG used post-CPB	32/32	——
NTG dose after CPB (μg/min)	40 (25)	10-100
Epinephrine dose after CPB (μg/min)	0 53 (1 7)	0-8 0
Temp during CPB (°C)	31 3 (1 2)	28 5-33 9
Urine volume after CPB (mL)	690 (590)	200-2700
Urine volume, 6 h after CPB (mL)	1140 (590)	300-2790

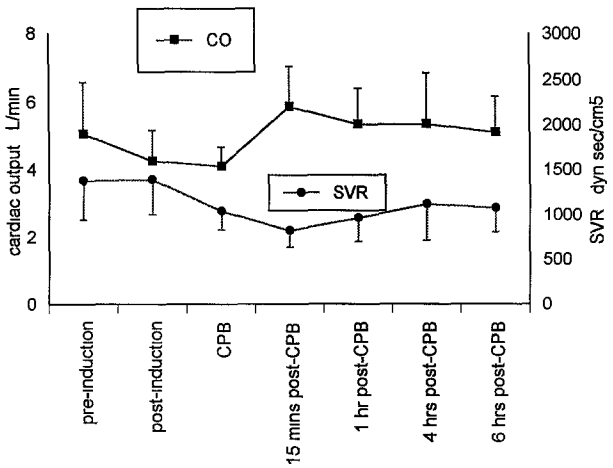

Fig 1. Perioperative changes in cardiac output and systemic vascular resistance. Mean and 1 SD

cant changes in DO_2, VO_2, and ER over the perioperative period (all $p < 0.001$).

There was a significant association between each SVR reading after CPB and its preceding measurement: 15 minutes post-CPB: 1 hour post-CPB, $r = 0.76$ ($p < 0.001$); 1 hour post-CPB, 4 hours post-CPB, $r = 0.65$ ($p < 0.001$); 6 hours post-CPB, 4 hours post-CPB, $r = 0.81$ ($p < 0.001$). Using regression analysis, the SVR measurement at 6 hours post-CPB could be predicted from that measured at 1 hour post-CPB (ie, approximately at the time of ICU admission) by the following regression equation:

$$\text{SVR(6 h post-CPB)} = 430 + 0.67 \times \text{SVR(1 h post-CPB)}, r^2 = 0.42, p < 0.001.$$

There was no significant correlation between SVR measurements and serum lactate, pHi, or endotoxin levels. A moderate negative correlation was found between the SVR and SvO_2 at 4 hours post-CPB ($r = -0.43, p < 0.01$) and at 6 hours post-CPB ($r = -0.52$, $p < 0.01$). There was also correlation between SVR and the oxygen ER at the same time points ($r = 0.43, p < 0.01$; $r = 0.52, p < 0.01$, respectively). There was no significant correlation between these factors and earlier SVR measurements. There was a consistent trend for a negative correlation between serum lactate and pHi measurements, but this was only significant at the pHi reading at 6 hours post-CPB ($r = -0.51$, $p < 0.01$). There was no correlation between pHi and endotoxin levels, VO_2, DO_2, oxygen ER, or cardiac output; nor was there a correlation between aortic cross-clamp time and endotoxin levels or SVR post-CPB.

DISCUSSION

The authors studied a group of elective cardiac surgical patients with intensive monitoring of hemodynamics, VO_2 and DO_2, pHi, serum lactate, and endotoxin levels. The study did not find any relationship between the SVR and endotoxin levels, although it was possible to derive a regression equation that predicted the SVR at 6 hours, from the SVR reading at 1 hour after CPB (at a time when the patient is preparing to leave the operating room). This may be useful in detecting those patients with low SVR at an earlier time and may promote earlier intervention with vasoconstrictor or inotrope therapy. It may also be useful in the future, when the underlying cause, or causes, of the low SVR syndrome are elucidated. It was hypothesized that intestinal ischemia and leakage of endotoxin through the bowel wall may be the underlying mechanism causing the low SVR syndrome. Although the study did not demonstrate this, it also did not demonstrate significant intestinal ischemia, as measured by pHi. It is possible that a larger study may detect more patients with frank intestinal ischemia and may detect more episodes of endotoxemia, which may lead to low SVR. It is also possible that some patients had episodes of regional ischemia, not detected by SvO_2 because of systemic dilution.

However, there was a relationship between SVR and SvO_2, which suggests that low SVR is an indicator of poor peripheral perfusion. It must be remembered that association does not imply causation, and, therefore, low SVR may follow some other end point of peripheral ischemia. This is supported by increased oxygen extraction and serum lactate, which are conventional indicators of inadequate tissue oxygen delivery. The significant changes in VO_2 and oxygen ER that were found, particularly after CPB, suggest that DO_2 should be maintained, by maximizing cardiac output, oxygen saturation, and hemoglobin concentration. The hemodiluted state after CPB may limit DO_2; therefore, it is

Table 2. Hemodynamic Changes Perioperatively

Time Period	Pre-Induction	30 min Postinduction	During CPB	15 Min Post-CPB	1 h Post-CPB	4 h Post-CPB	6 h Post-CPB
CO (L/min)	5 07 (1.53)	4.26 (0 92)	4 10 (0 57)	5 87 (1.2)	5.35 (1 1)	5.36 (1 5)	5 11 (1.1)
	3 31-9 21	2.67-6 33	3 00-5.50	2.94-8 80	2.91-7 40	2 98-9.45	3.47-7.43
SVR (dyn/s/cm^{-5})	1382 (431)	1391 (383)	1041 (210)	823 (181)	963 (263)	1120 (406)	1076 (267)
	602-2350	821-2401	603-1581	574-1387	598-1621	668-2093	656-1890
MAP (mmHg)	88 (15)	77 (10)	55 (9 7)	66 (8.0)	69 (7.0)	78 (9.6)	75 (7.4)
	53-108	57-98	40-90	48-82	55-83	57-98	64-95
PCWP (mmHg)	10 (4)	9 3 (4)	——	11 (4)	10 (3)	9.5 (3)	10 (3)
	3-21	4-23	——	4-20	3-16	6-15	6-19

Abbreviations: CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CPB, cardiopulmonary bypass

Mean (SD) and Range

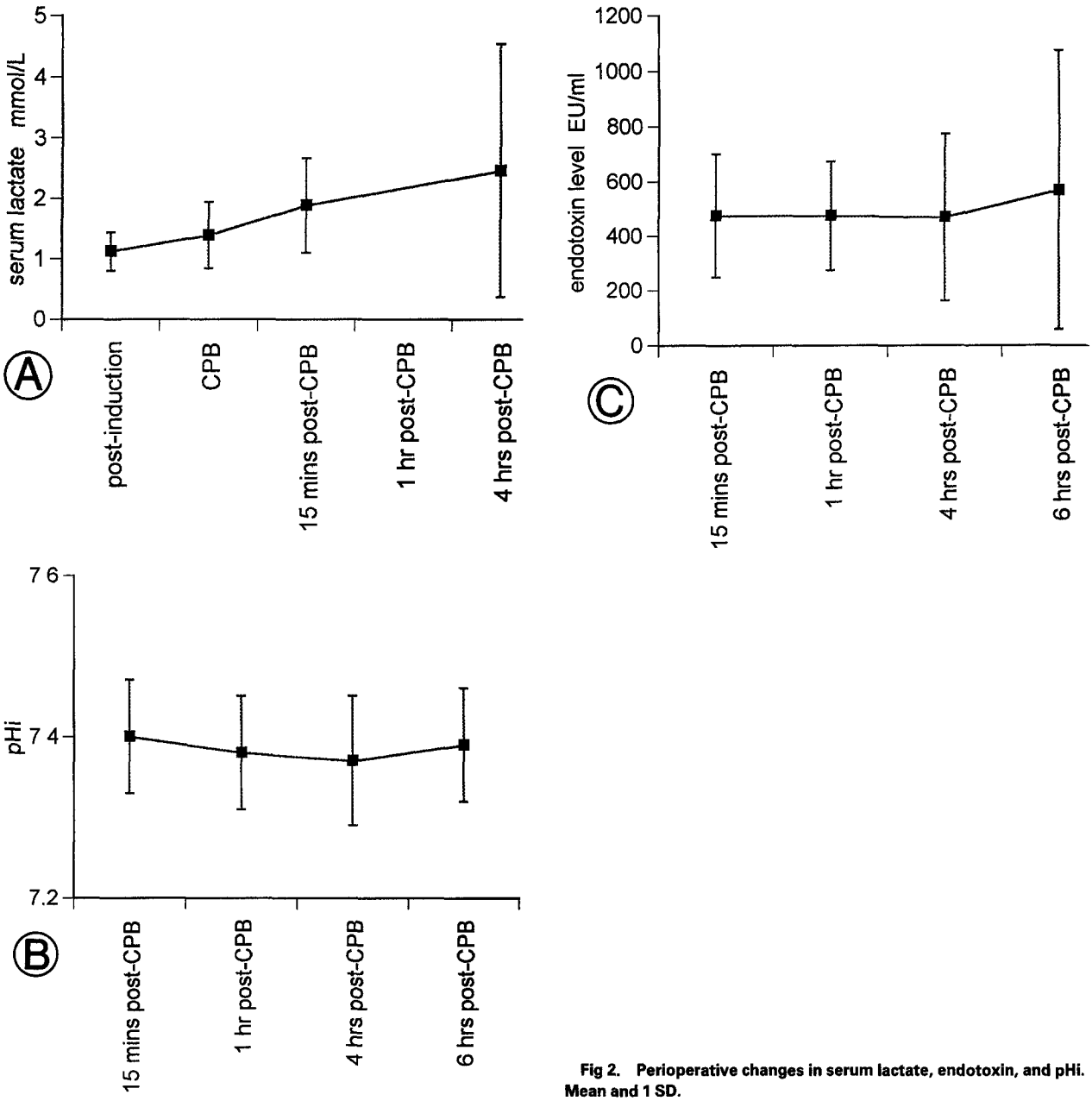

Fig 2. Perioperative changes in serum lactate, endotoxin, and pHi. Mean and 1 SD.

particularly important that cardiac output is maintained during this period. Correction of dilutional anemia with a concentrated red cell transfusion will not only increase DO_2 but will also increase plasma viscosity and SVR. This may be one of the explanations for the association between low SVR and SvO_2. The substantial increase in VO_2 that occurs after CPB may add support to continuing mechanical ventilation until oxygen ER returns to baseline, as this has been shown to reduce VO_2.[15] Interestingly, this elevated ER may persist longer than 24 hours.[16]

The decrease in SVR that occurred during CPB, with gradual resolution after CPB, is probably caused by hemodilution and may not indicate any significant change in vascular tone.[17] Although the increase in cardiac output may reflect increased myocardial performance after surgical correction of coronary artery disease, it is more likely a reflection of the increased metabolic demands illustrated by the changes in VO_2 and ER. This may be related to a subclinical oxygen debt built up during CPB, particularly within the gastrointestinal tract.[12-14,18] It is also a time of restoration of body temperature, return to spontaneous ventilation, pain, and the neurohumoral response to major surgery.[19,20] Other vasoactive substances (complement C3a and C5a, granulocyte elastase, interleukins 6 and 8) have been described after CPB, which may also promote excessive vasodilation and appear to be related to aortic cross-clamp time.[10,21,22] It is likely that endothelial infiltration by these substances can produce a state of resistant vasodila-

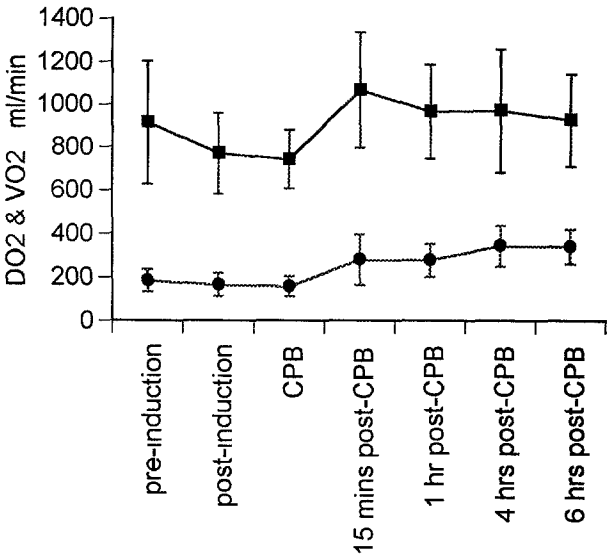

Fig 3. Perioperative changes in DO_2 and VO_2. Mean and 1 SD.

tion and may also participate in myocardial reperfusion injury, although the role of endotoxin in their production after CPB remains obscure.[10,21,22]

Does DO_2 determine VO_2? The existence of pathologic oxygen supply dependence is controversial,[23] although there is some evidence of its existence in dogs receiving endotoxin.[24] This is supported by Ohri et al who found that VO_2 and ER increased markedly during the rewarming phase of CPB.[25] This suggests that endotoxemia may impair peripheral oxygen extraction, although oxygen ER in excess of 0.5 can be maintained before oxygen supply dependence is demonstrated.[24] Nelson et al have argued that oxygen supply dependence follows derangement of normal endothelial control of blood flow and that endotoxins are known to damage endothelium.[24] Subsequent uncontrolled release of substances such as nitric oxide and acetylcholine from the endothelium may generate the low SVR occasionally observed after CPB. Other authors have raised doubts as to the validity of calculated VO_2 and DO_2.[23] When compared with measured VO_2, derived from inspired and expired gas concentrations, Manthous et al could not find any relationship between VO_2 and cardiac output in patients with septic shock.[23] However, the present patient population differs from critically ill patients with adult respiratory distress syndrome and would not be expected to have such a discrepancy between measured and calculated VO_2. A recent report by Routsi et al found a strong relationship between VO_2 and DO_2,[16] but they did not account for the statistical property of mathematical coupling,[26] where both are calculated using the common terms of cardiac output and hemoglobin concentration ensuring a good correlation, irrespective of their true relationship. However, they also found a relationship between serum lactate and SvO_2, although they measured PvO_2.[24]

Measurement of pHi has also been promoted as a monitor of tissue perfusion in critically ill patients, including those after cardiac surgery.[9,14,18,25,27] Nevertheless, other authors argue that conventional blood-gas analysis provides similar information.[28] The present results are in agreement with previous studies, but this study did not find dramatic changes after CPB. Gaer et al found that pulsatile flow preserved pHi during CPB, when compared with nonpulsatile flow, but this may reflect the lower temperature used during CPB (28°C) or inferior CPB technique, although their small numbers ($n = 10$) make interpretation difficult.[14] Anderson et al found that pHi was low immediately after CPB but also could not find a relationship between pHi and endotoxin levels.[9]

The authors are unsure of the usefulness of measuring pHi in cardiac surgical patients, and at this time, considering the cost implications, would not recommend gastric tonometry for routine monitoring. Although some patients had low cardiac output and mixed venous oxygen desaturation, no relationship between these conventional indicators of poor peripheral perfusion and pHi was found. However, there was a moderate relationship between pHi and serum lactate at 6 hours after CPB, which may indicate poor perfusion. This is known as a type I lactic acidosis; however, there is also a type II lactic acidosis that is not related to poor peripheral perfusion. Raper et al have described elevated serum lactate with adequate peripheral perfusion after cardiac surgery.[29] They argue that lactate may be released from leg muscles and that catecholamines may promote its peripheral release. Manthous et al state that the increased serum lactate concentrations may also be a reflection of pyruvate accumulation[23]; this may be secondary to reduced hepatic clearance during or after CPB. However, other authors have found increased intestinal production of lactate during CPB, which may reflect transient intestinal ischemia.[30] It is arguable that conventional measures of tissue perfusion, such as cardiac output, SvO_2, and DO_2 may lack specificity, such that regional (eg, intestinal) ischemia may coexist.

Endotoxemia has been found after CPB.[6-10] Other authors dispute these findings, arguing that the methods used have not been validated.[8,22] Inaba et al compared two different endotoxin assay techniques after cardiac surgery and found a wide discrepancy between them.[22] This study used a chromogenic limulus lysate assay, a widely used method in cardiac surgery, but the authors are unsure of how specific currently available endotoxin assays are. Although the endotoxin levels were high in some patients after CPB, they were not related to hemodynamic changes or pHi. Thus, the importance of high endotoxin levels remains to be determined. Nilsson et al suggested that contamination from CPB circuitry, gloves, and heparin may be extraneous sources of endotoxin.[8] Taggart et al also found a small increase in endotoxin levels after CPB, but these did not correlate with complement levels or white blood cell count.[10] They also could not find a relationship between endotoxin levels and duration of CPB. Blanot et al studied patients during liver transplantation, who have also been found to suffer a "post-perfusion syndrome"[31] similar to the low SVR syndrome described after CPB. As with this

study, they could not find an association with endotoxin levels.

The metabolic and hemodynamic changes that occur after cardiac surgery require close attention to a variety of calculated and measured variables. There have been some recent innovations in this area, but this study could not find any added value in their use. The authors could not find an association between low SVR and intestinal ischemia (as measured by pHi) or endotoxemia. It is concluded that oxygen delivery, through optimizing oxygenation and cardiac output, remains important during and after cardiac surgery. Other parameters may have a role to play in perioperative monitoring for cardiac surgery but should not replace current established endpoints of therapy.

ACKNOWLEDGMENT

The authors would like to thank Jenny Ingram, Microbiologist, for the endotoxin assay, and Nina Davidson, senior scientist, Microbiology Unit, for her assistance and provision of technical support. They would also like to thank the nursing staff in the Cardiothoracic ICU for their dedicated commitment to the trial requirements.

REFERENCES

1. Thaker U, Geary V, Chalmers P, et al: Low systemic vascular resistance during cardiac surgery· Case reports, brief review, and management with angiotensin II. J Cardiothorac Vasc Anesth 4:360-363, 1990

2 Myles PS, Olenikov I, Bujor MA, et al: ACE-inhibitors, calcium antagonists and low systemic vascular resistance following cardiopulmonary bypass. A case-control study. Med J Aust 158:675-677, 1993

3. Suffredini AF, Fromm RE, Parker MM, et al: The cardiovascular response of normal humans to the administration of endotoxin. N Engl J Med 321:280-287, 1989

4. Balk RA. Septic shock: Pathophysiology. Curr Opin Anaesthesiol 7.136-140, 1994

5. Hurley JC: Reappraisal of the role of endotoxin in the sepsis syndrome. Lancet 341.1133-1135, 1993

6. Andersen LW, Baek L, Degn H, et al: Presence of circulating endotoxins during cardiac operations J Thorac Cardiovasc Surg 93:115-119, 1987

7. Rocke DA, Gaffin SL, Wells MT, et al: Endotoxemia associated with cardiopulmonary bypass. J Thorac Cardiovasc Surg 93:832-837, 1987

8. Nilsson L, Kulander L, Nystrom SO, et al: Endotoxins in cardiopulmonary bypass. J Thorac Cardiovasc Surg 100.777-780, 1990

9. Andersen LW, Landow L, Baek L, et al· Association between intramusosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor concentrations in patients undergoing cardiopulmonary bypass Crit Care Med 21:210-217, 1993

10. Taggart DP, Sundaram S, McCartney C, et al: Endotoxemia, complement, and white blood cell activation in cardiac surgery· A randomized trial of laxatives and pulsatile perfusion Ann Thorac Surg 57:376-382, 1994

11. Fiddian-Green RG: Gut mucosal ischemia during cardiac surgery. Sem Thorac Cardiovasc Surg 2·389-399, 1990

12. Baue AE: The role of the gut in the development of multiple organ dysfunction in cardiothoracic patients. Ann Thorac Surg 55:822-829, 1993

13. Ohri SK, Bjarnason I, Pathi V, et al· Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability. Ann Thorac Surg 55:1080-1086, 1993

14. Gaer JAR, Shaw ADS, Wild R, et al: Effect of cardiopulmonary bypass on gastrointestinal perfusion and function Ann Thorac Surg 57:371-375, 1994

15. Prakash O, Meij SH· Oxygen consumption and blood gas exchange during controlled and intermittent mandatory ventilation after cardiac surgery. Crit Care Med 13:556-559, 1985

16. Routsi C, Vincent J-L, Bakker J, et al: Relation between oxygen consumption and oxygen delivery in patients after cardiac surgery. Anesth Analg 77:1104-1110, 1993

17. Himpe D· New approach to systemic vascular resistance calculation and clinical decision making. Acta Anaesth Belg 41:291-295, 1990

18. Niinimikoski J, Kuttila K. Adequacy of tissue oxygenation in cardiac surgery: Regional measurements. Crit Care Med 21:S77-S83, 1993

19. Udelsman R, Norton JA, Jelenich SE, et al: Responses of the hypothalamic-pituitary-adrenal and renal-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. J Clin Endocrinol Metab 64:986-994, 1987

20. Tulla H, Takala J, Alhava E, et al. Hypermetabolism after coronary artery bypass J Thorac Cardiovasc Surg 101:598-600, 1991

21. Kawamura T, Wakusawa R, Okada K, et al: Elevation of cytokines during open heart surgery with cardiopulmonary bypass· Participation of interleukin 8 and 6 in reperfusion injury. Can J Anaesth 40:1016-1021, 1993

22. Inaba H, Kochi A, Yorozu S· Suppression by methylprednisolone of augmented plasma endotoxin-like activity and interleukin-6 during cardiopulmonary bypass. Br J Anaesth 72:348-350, 1994

23 Manthous CA, Schumacker PT, Pohlman, et al: Absence of supply dependence of oxygen consumption in patients with septic shock. J Crit Care 8:203-211, 1993

24. Nelson DP, Samsel RW, Wood LDH, et al: Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxemia. J Appl Physiol 64:2410-2419, 1988

25. Ohri SK, Keogh BE, Becket J, et al: The effects of cardiopulmonary bypass upon gut blood flow, oxygen utilisation and intramucosal pH in a canine model· implications for gut barrier function. Proceedings of 14th Annual San Diego Cardiothoracic Surgical Symposium Pathophysiology and Techniques of Cardiopulmonary Bypass XIV: 231, 1994

26 Archie JP. Mathematical coupling of data. A common source of error. Ann Surg 193 296-303, 1981

27. Gutierrez G, Palizas F, Doglio G, et al· Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339:195-199, 1992

28 Boyd O, Lamb G, Bland JM, et al: Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. Lancet 341:142-146, 1993

29 Totaro RJ, Raper R: Lactic acidosis post cardiopulmonary bypass. Randomised prospective study of adrenaline and noradrenaline as causative factors. Anaesth Intens Care 22:220, 1994

30. Landow L: Splanchnic lactate production in cardiac surgery patients. Crit Care Med 21·S84-S91, 1993

31. Blanot S, Gillon MC, Ecoffey C, et al: Circulating endotoxins during orthotopic liver transplantation and post-reperfusion syndrome Lancet 342·859-890, 1993 (letter)