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## Bedside Monitoring of Cerebral Energy State During Cardiac Surgery—A Novel Approach Utilizing Intravenous Microdialysis

Simon Mølström, MD,\* Troels H. Nielsen, MD, PhD,† Claus Andersen, MD, PhD,‡ Carl H. Nordström, MD, PhD,† and Palle Toft, MD, PhD, DMSc\*

**Objectives:** This study investigated whether the lactate-to-pyruvate (LP) ratio obtained by microdialysis (MD) of the cerebral venous outflow reflected a derangement of global cerebral energy state during cardiopulmonary bypass (CPB).

**Design:** Interventional, prospective, randomized study.

**Setting:** Single-center, university teaching hospital.

**Participants:** The study included 10 patients undergoing primary, elective coronary artery bypass grafting.

**Interventions:** Patients were randomized blindly to low mean arterial pressure (MAP) (40–60 mmHg; n = 5) or high MAP (60–80 mmHg; n = 5) during CPB. The MD catheters were positioned in a retrograde direction into the jugular bulb, and a reference catheter was inserted into the brachial artery. The correlations among LP ratio, MAP, data obtained from bifrontal near-infrared spectroscopy (NIRS), and postoperative neurologic outcome measures were assessed.

**Measurements and Main Results:** The correlated difference between pooled LP ratio (low and high MAP) of the

jugular venous and the arterial blood was significant (LP<sub>arterial</sub> 17 [15–20] v LP<sub>venous</sub> 26 [23–27]; p = 0.0001). No cerebral desaturations (decrease in rSO<sub>2</sub> > 20% from baseline) were observed in either group during CPB. In each group, 50% of the patients showed significant cognitive decline (minimal state examination, 3 points) 2 days after surgery.

**Conclusion:** The LP ratio of cerebral venous blood increased significantly during CPB, indicating compromised cerebral oxidative metabolism. Conventional monitoring of rSO<sub>2</sub> by NIRS did not show a corresponding decrease in cerebral oxygenation. As the patients exhibited decreased cognitive functions after CPB, increases in jugular venous LP ratio may be a sensitive indicator of impending cerebral damage.

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**KEY WORDS:** cardiac surgery, cardiopulmonary bypass, microdialysis, regional cerebral oxygen saturation, cerebral oxidative metabolism, neurologic outcome

Despite considerable progress in surgical cardiopulmonary bypass (CPB) and anesthetic techniques, brain damage remains an important complication of cardiac surgery.<sup>1,2</sup> Recent studies report post-coronary artery bypass grafting (CABG) stroke rates of 1% to 5%.<sup>3</sup> Delirium and postoperative cognitive dysfunction remain important problems that can affect more than half of patients, although they may resolve spontaneously in as many as 50% of those affected.<sup>4</sup> A number of pathophysiologic processes underlie the neurologic complications, which necessitate a multifaceted therapeutic approach.<sup>2,5</sup> The authors present a novel technique for detecting threatening intraoperative neurologic complications: evaluation of cerebral energy state obtained by the microdialysis (MD) technique and biochemical analysis of the cerebral venous outflow.

Although the combined results of various studies have indicated that an intraoperative mean arterial pressure (MAP) higher than 80 mmHg might reduce neurologic complications, differing opinions remain.<sup>6–9</sup> Low-risk patients tolerate MAPs of 50-to-60 mmHg without evident complications, although limited data suggest that higher-risk patients may benefit from MAP > 70 mmHg.<sup>10</sup> Intraoperative cerebral monitoring offers a possibility to individualize and optimize conditions during CPB and surgery. Near-infrared spectroscopy (NIRS) is a technique frequently used to measure cerebral oxygenation (rSO<sub>2</sub>). Intraoperative cerebral oxygen desaturation has been reported to be associated significantly with an increased risk of cognitive decline and prolonged hospital stay after CABG, and monitoring cerebral rSO<sub>2</sub> was shown to be associated with fewer incidences of major organ dysfunction.<sup>11,12</sup> However, in a large systematic review, it was concluded that only low-level evidence linked low rSO<sub>2</sub> during cardiac surgery to postoperative neurologic complications.<sup>13</sup>

Cerebral energy state is dependent entirely on oxidative metabolism, which is reflected immediately in cerebral cytoplasmic redox state. Under clinical conditions, cerebral cytoplasmic redox state conventionally is evaluated from the lactate-to-pyruvate (LP) ratio obtained from intracerebral MD and bedside biochemical analysis. The ratio increases instantaneously when energy metabolism is compromised.<sup>14</sup> Due to monocarboxylic acid transporters, lactate and pyruvate readily pass cellular membranes.<sup>15</sup> The change in cytoplasmic LP ratio is detected immediately by interstitial MD.<sup>16</sup> In an experimental study, the authors have shown recently that a global decrease in cerebral oxygenation due to a pronounced decrease in MAP was reflected in an increased LP ratio of the draining venous blood.<sup>17</sup> Accordingly, by adopting this technique, it might be possible to evaluate whether cerebral cytoplasmic redox state is affected during CPB and CABG in patients.

By utilizing intracerebral MD, the upper normal limit for the LP ratio of normal human brain has been defined as 30.<sup>18,19</sup> An LP ratio above this level indicates either hypoxia/ischemia or

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mitochondrial dysfunction. In this pilot study, an evaluation of global cerebral energy state from MD catheters positioned in the internal jugular vein in 10 patients undergoing CABG and CPB was presented.

The patients were randomized into 2 groups, with a MAP of either 40-to-60 mmHg (low MAP) or 60-to-80 mmHg (high MAP). The results from the biochemical monitoring were compared with simultaneously performed bifrontal NIRS. Furthermore, as the decrease in MAP during CPB affected all tissues, the LP ratio obtained in the jugular venous blood was compared with that obtained in the arterial blood to document that an observed change in jugular LP ratio originated from a change in cerebral redox state.

## METHODS

This feasibility randomized study was designed to determine the yield of bedside monitoring of cerebral energy state during cardiac surgery utilizing intravenous MD. A total of 10 patients undergoing primary, nonemergency CABG were randomized blindly to a low MAP (40-60 mmHg,  $n = 5$ ) or a high MAP (60-80 mmHg,  $n = 5$ ) group during CPB. The association among biochemical MD parameters, MAP, the data obtained from simultaneously bifrontal NIRS, and postoperative neurologic outcome measures, (mini-mental state examination [MMSE]), was assessed.

### Inclusion Criteria and Management Protocol

Ten patients aged  $>60$  years, who were scheduled to undergo elective CABG on CPB, were enrolled in the study from February to April 2015. All participants received written information about the study and provided informed consent. Acute patients or reoperations, as well as patients with an epidural catheter, previous stroke, stenotic carotids, diabetes mellitus, ejection fraction  $<50\%$ , elevated preoperative serum creatinine above 200  $\mu\text{M}$ , or an estimated preoperative risk of  $>5\%$ , were excluded. Classification of stroke and carotid stenosis was based on clinical examination and case history, but no specific investigations were performed to exclude the possibility of a previous stroke or carotid stenosis.

A protocol for anesthetic management of the participants was designed to ensure uniform conduction of the procedure. Anesthesia was induced with sufentanil (50-100  $\mu\text{g}$ ) followed by propofol (150-300 mg). Relaxant was administered afterward, and the patients were intubated. Sevoflurane (2%) and sufentanil were used for maintenance of anesthesia. During mechanical ventilation,  $\text{PaO}_2$  was maintained at 17.0-to-22.0 kPa,  $\text{PaCO}_2$  at 5.0-to-5.3 kPa, pH at 7.35-to-7.43, and hematocrit at  $>22$ .

The standard CPB equipment consisted of a Stöckert S5 heart-lung machine with roller pumps (Sorin) with medium occlusion settings. Dideco tubings with a Compactflo Evo adult membrane oxygenator and a Micro 40 adult arterial filter D734 (Sorin) were primed with 1,800-mL of Ringer's lactate solution (Fresenius Kabi) including 5,000 IU of heparin in an open system. Harefield cardioplegia solution was mixed with blood in a 1:4 ratio and administered cold at  $5^\circ\text{C}$  using a Sorin

cardioplegia heat exchanger CSC14. A triple-transducer set, DTX Plus (Argon), was used for preoxygenator, postoxygenerator, and cardioplegia pressure monitoring.

A MAP target of either 40-to-60 mmHg (low MAP) or 60-to-80 mmHg (high MAP) in accordance with clinical routine at the department was achieved via inotropic support (metaxalone, norepinephrine  $<0.30 \mu\text{g}/\text{kg}/\text{min}$ ) when needed. The blood glucose level was kept between 5 and 8 mmol/L. During CPB, the calculated flow was 2.4 L/min/m<sup>2</sup> and was maintained at the same level unless SvO<sub>2</sub> declined below 65%. The temperature target was  $37.0^\circ\text{C}$  initially and during CPB.

### Monitoring

Vital functions were monitored according to general practice. Average MAP was measured at 20-minute intervals during CPB. Diuresis was measured hourly. Core temperature was recorded in the bladder. Blood glucose was monitored by repeated arterial blood samples.

Regional cerebral oxygen saturation was monitored using bifrontal NIRS (Somanetics INVOS Cerebral Oximeter system). Right and left frontal rSO<sub>2</sub> values were recorded simultaneously preoperatively and intraoperatively and for 2 hours postoperatively. Cerebral desaturation was defined as a decrease in the relative rSO<sub>2</sub> value of 20% compared with the individual preinduction baseline value.<sup>13</sup> Values were recorded every 20 minutes.

An MD catheter (70, MDialysis AB, Stockholm, Sweden) was placed in a retrograde direction into the jugular bulb. A second identical MD catheter was inserted into one brachial artery. Both catheters were inserted through a peripheral intravenous 17-G cannula using ultrasound guidance. The positioning of the catheter in the jugular bulb above the inlet of the common facial vein was verified on lateral neck radiograph, according to accepted principles.<sup>20</sup>

The MD catheters were perfused by MD pumps (106, MDialysis AB) at 0.3  $\mu\text{L}/\text{min}$ . The perfusates were collected in microvials and were analyzed every 20 minutes by enzymatic photometric techniques and displayed bedside (Iscus, MDialysis AB). The analyses included variables that were monitored routinely during intracerebral MD: glucose, pyruvate, lactate, glutamate, and glycerol.

### Evaluation of Outcome

Cognitive function was assessed via the MMSE.<sup>21</sup> Patients were assessed preoperatively and on postoperative day 2 after surgery. The MMSE provides measures of orientation, registration (immediate memory), short-term memory (but not long-term memory), and language functioning and was used to indicate the presence of cognitive impairment.<sup>22</sup> The MMSE has been used to determine the relationship between changes in blood pressure during CABG surgery and early cognitive dysfunction. A drop in MAP from a preoperative baseline was associated with risk for early cognitive dysfunction after CABG surgery.<sup>22,23</sup> The National Institute for Health and Care Excellence classifies an MMSE score 21-to-24 as mild, 10-to-20 as moderate, and  $<10$  as severe impairment.<sup>24</sup>

## Statistical Analysis

All data are presented as median and interquartile range. When the means of 2 groups were compared, a Student t-test was used. One-way analysis of variance (ANOVA) was corrected for multiple comparisons using the Bonferroni test ( $\alpha = 0.006$ ) and was used to compare the means of 3 or more groups. Repeated-measures ANOVA was used to assess the statistical significance of differences between the repeated recording times for MD-cerebral venous outflow, MD-arterial, hemodynamic parameters, NIRS data, and MMSE data. Linear regression was used to model the level or change in jugular bulb LP ratio at each time point as a function of the level or change in cerebral saturations, and the coefficient of determination ( $R^2$ ) was estimated. Statistical significance was set at  $p < 0.05$ . Statistical analyses were calculated, and trend curves displaying MD data, MAP, and LP ratios were illustrated with linear plots built in Graph Pad Prism 6.0 (GraphPad Software Inc., 2014).

## Ethics

The Danish Regional Committee on Health and Research Ethics and Danish Data Protection Agency approved the study (trial registration: S-20130166). The study complied with the Helsinki declaration (trial register: ClinicalTrials.gov NCT02846818).

## RESULTS

All 10 patients completed the entire protocol. One patient in the low-MAP group had a number of MD-arterial data excluded due to technical problems with the MD catheter.

Table 1 shows baseline clinical characteristics of the patients prior to CPB and perioperative data. There were no significant differences between the 2 study groups regarding baseline physiologic variables and the American Society of Anesthesiologists score. The durations of CPB and the aortic cross-clamp application were comparable. The mean CPB time was 102 (low MAP) and 92 minutes (high MAP), with an ischemic time of 60 and 56 minutes to accomplish a mean of 3.8 and 2.8 grafts/patient, respectively. Calculated flow during CPB normalized for body surface area was identical in the 2 groups. Intraoperatively, the means of PaCO<sub>2</sub> over the period of CPB were nonsignificantly different between groups. All patients in both groups showed an increase in LP ratio during CPB. The rSO<sub>2</sub> obtained by NIRS did not indicate cerebral desaturations in either group during CPB.

There was no in-hospital or 30-day mortality, nor were there any perioperative strokes in the groups. The mean postoperative hospital length of stay was 4.6 and 5.4 days, respectively.

## MAP

In both groups, all patients achieved the target MAP and remained stable during CPB. In the high-MAP group (60-80 mmHg), the target pressure was reached within a few minutes after CPB initiation. Significant differences were observed between the 2 groups when comparing perfusion pressure during the entire CPB period (Fig 1B). During CPB, including all brief periods of low flow, median MAP was 44 (interquartile range, 41-49) mmHg for the low-MAP group and 65 (60-76)

**Table 1. Baseline Characteristics and Perioperative Data of the Two MAP Groups Undergoing CABG and CPB**

Characteristic	Low-MAP Group	High-MAP Group
	(N = 5) Median [IQR]	(N = 5) Median [IQR]
<b>Demographics</b>		
Age (years)	69 [66–72]	72 [72–77]
Sex	5 M	4 M, 1 F
BMI (kg/m <sup>2</sup> )	25 [23–27]	25 [24–30]
<b>Clinical factors</b>		
Baseline MAP (mmHg)	88 [87–93]	93 [88–94]
Baseline NIRS left side (%)	73 [68–82]	68 [68–71]
Baseline NIRS right side (%)	75 [68–83]	67 [65–68]
Baseline hematocrit	0.43 [0.42-0.44]	0.40 [0.42-0.44]
Baseline MMSE	25 [25]	25 [24,25]
<b>Intraoperative</b>		
CPB duration (min)	106 [80–123]	95 [89–105]
Calculated flow (L/min)	4.5 [4.4-4.9]	4.6 [4.5-5.0]
Cross-clamp duration (min)	56 [51–71]	52 [44–66]
Number of grafts	3 [3–5]	3 [3,4]
Fluid balance (mL)	2,575 [1,585]	2,080 [410]
Metaxidrine (mg)	1.10 [0.80-1.10]	1.10 [1.0-1.5]
Norepinephrine (mg)	0.36 [0.26-0.39]	1.10 [0.93-1.83]
MAP (mmHg)-CPB	43 [40–47]	65 [60–76]
Lowest hematocrit	0.27 [0.26-0.28]	0.30 [0.27-0.30]
<b>Postoperative factors</b>		
Total LOS (days)	5.0 [5.0-5.0]	6.0 [5.0-7.0]
MMSE	23 [22,23]	21 [20–22]

NOTE. NIRS was measured as regional saturation (rSO<sub>2</sub>).

Abbreviations: BMI, body mass index; CPB, cardiopulmonary bypass; IQR, interquartile range; LOS, length of stay; MAP, mean arterial pressure; MMSE, mini-mental state examination; NIRS, near-infrared spectroscopy.

mmHg for the high-MAP group ( $p < 0.001$ ) (Fig 1B). The high-MAP group received significantly higher mean doses of norepinephrine compared with the low-MAP group ( $p = 0.04$ ).

## MD—LP Ratio

After initiating CPB, the mean LP ratio obtained from MD of the internal jugular vein increased significantly by 160% (low MAP) and 130% (high MAP). In both groups, the mean peak LP ratio increased significantly from baseline during CPB (11 [10–14] to 29 [23–36];  $p = 0.02$  and 13 [11–15] to 25 [17–34];  $p = 0.02$ ) for low and high MAP, respectively. There was no difference between groups regarding venous outflow LP ratio during CPB, although low-MAP patients had a tendency to have higher LP ratios (Fig 2A). In both groups, LP ratio returned to baseline after CPB.

Arterial LP ratio increased in both groups during CPB, but no significant change from baseline was observed. There was no significant difference between the venous outflow LP ratio during CPB and the corresponding arterial LP ratio in the low-MAP group, but significance was reached in the high-MAP group (25 [24–27] and 17 [15–18];  $p = 0.0001$ ) for LP<sub>venous</sub> and LP<sub>arterial</sub>, respectively.

The correlated difference between pooled LP ratio (low and high MAP) of the jugular venous blood and the arterial blood was significant (LP<sub>arterial</sub> 17 [15–20] v LP<sub>venous</sub> 26 [23–27];  $p = 0.0001$ ) (Fig 1A).

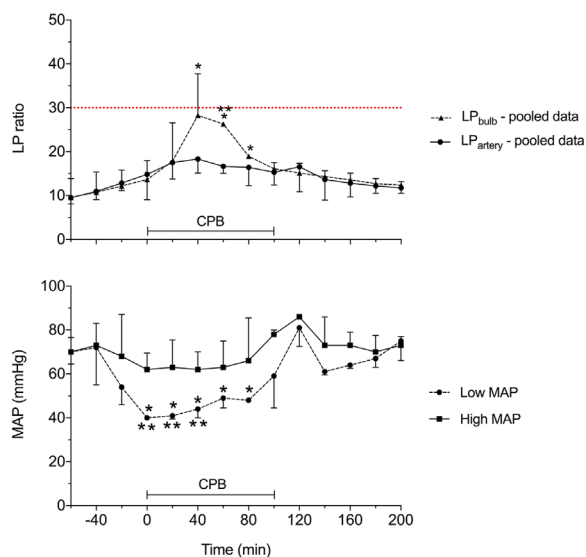
### MD—Glucose, Pyruvate, Lactate, Glycerol, Glutamate

In both groups, the glucose obtained in the jugular bulb increased significantly from 5.0 (4.9-5.4) mM to 6.5 (6.3-6.8) mM for low MAP ( $p = 0.045$ ) and 6.1 (4.9-7.1) mM to 7.9 (7.4-8.5) mM for high MAP ( $p = 0.03$ ). During CPB, the high-MAP group showed a greater tendency to increase in glucose, but this change was not significant compared to the low-MAP group. A significant increase in pyruvate was observed concomitantly; from 79 (71-80)  $\mu\text{M}$  to 147 (146-148)  $\mu\text{M}$  for low MAP ( $p = 0.03$ ) and 81 (73-96)  $\mu\text{M}$  to 125 (103-140)  $\mu\text{M}$  for high MAP ( $p = 0.02$ ).

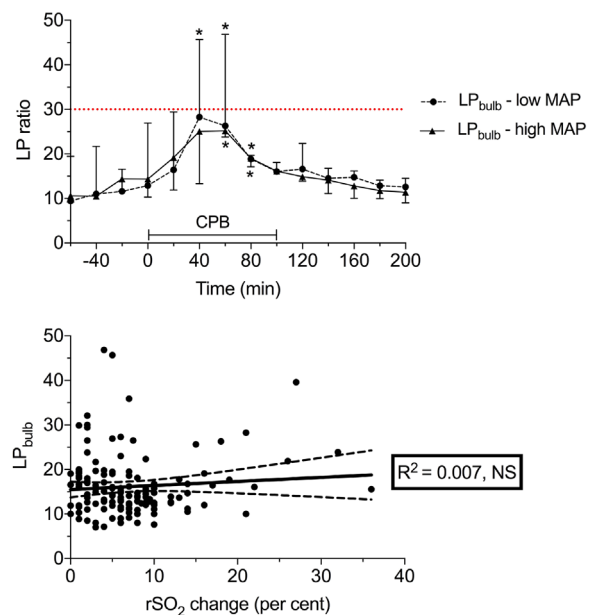
Glucose and pyruvate exhibited parallel changes during CPB, and the high levels remained stable during the study period (Table 2). The differences between the groups of high and low MAP were statistically nonsignificant. During CPB, jugular venous lactate peaked at 3.5 (3.3-4.0) mM for the low-MAP group and 3.4 (3.0-3.8) mM for the high-MAP group. In both groups, lactate returned to baseline after CPB. The lactate levels during CPB were not significantly different between the low- and high-MAP groups (one-way ANOVA analysis). Parallel increases were obtained for venous outflow (Table 2) and arterial glycerol levels during and immediately after CPB. During CPB, the arterial glutamate concentration was almost identical to the level obtained in the jugular bulb: 53 (50-57)  $\mu\text{M}$  and 54 (38-56)  $\mu\text{M}$ , respectively.

### NIRS

In the low- and high-MAP groups, the baseline right-side  $r\text{SO}_2$  values were 75% (68%-83%) and 67% (65%-68%),



**Fig 1. (A) Acute effects of cardiopulmonary bypass (CPB) on jugular bulb lactate-to-pyruvate (LP) ratio and peripheral artery LP ratio. (B) Corresponding mean arterial pressure (MAP). Global cerebral LP ratio above normal ( $>30$ ) indicated compromised energy metabolism.<sup>19</sup> There is a significant difference between low MAP and high MAP during CPB. The peak  $\text{LP}_{\text{bulb}}$  ratio in the jugular bulb was significantly higher than the corresponding  $\text{LP}_{\text{artery}}$  ratio. \*Significant difference from baseline. \*\*Significant difference between corresponding data points by one-way analysis of variance and corrected for multiple comparisons using the Bonferroni test ( $\alpha = 0.006$ ). Values are median and error with interquartile range ( $n = 10$ ).**



**Fig 2. (A) Acute effects of cardiopulmonary bypass (CPB) on data obtained from a microdialysis catheter, (lactate-to-pyruvate [LP] ratio), placed in the jugular bulb. (B) Predicted association between jugular bulb LP ratio and corresponding change in cerebral oxygen saturation ( $r\text{SO}_2$ ). Data shown are LP ratio - low mean arterial pressure (MAP) (dashed line) and LP ratio - high MAP (solid). The difference between groups was statistically nonsignificant. Linear regression was used to model the level or change in jugular bulb LP ratio at each time point as a function of the level or change in cerebral saturations,  $R^2$  value (0.007), indicating nonsignificant (NS) correlation. Cerebral desaturation ( $r\text{SO}_2$ ) was defined as a decrease in the relative  $r\text{SO}_2$  value of 20% compared with the individual pre-induction baseline value. \* Significant difference from baseline by one-way analysis of variance and corrected for multiple comparisons using the Bonferroni test ( $\alpha = 0.006$ ). Values are median and error with interquartile range ( $n = 10$ ).**

respectively. Baseline  $r\text{SO}_2$  values left side were 73% (68%-82%) and 68% (68%-71%) (Table 1). No cerebral desaturations (decrease in  $r\text{SO}_2 > 20\%$  from baseline) were observed in either group during CPB. The average decrease in the relative  $r\text{SO}_2$  values compared with the individual pre-induction baseline level were at the right side of the low-MAP group and high-MAP group 9% (4%-12%) and 5% (3%-10%), respectively. The corresponding decreases of the left-side  $r\text{SO}_2$  values were 6% (3%-12%) versus 4% (5%-12%). The correlation between jugular LP ratio and  $r\text{SO}_2$  was not significant ( $R^2 = 0.007$ ) (Fig 2B).

### MMSE

All patients were assessed preoperatively and on post-operative day 2. No difference in presurgery score was observed between the 2 groups (low MAP 25 [25]  $\nu$  high MAP 25 [24,25]). In each group, 50% of the patients showed significant cognitive decline (MMSE 3 points) 2 days after the surgery (low MAP,  $p = 0.002$ ; high MAP,  $p = 0.01$ ). Difference in MAP did not have a significant impact on cognitive function postoperatively (22 [21-23]  $\nu$  20 [19-22]).

Table 2. Biochemical Variables Obtained From Microdialysis Obtained in the Jugular Bulb During CABG and CPB

Elapsed Time (min)	LP Ratio		Lactate (mM)		Pyruvate (μM)		Glucose (mM)		Glycerol (μM)		Glutamate (μM)	
	Low MAP	High MAP	Low MAP	High MAP	Low MAP	High MAP	Low MAP	High MAP	Low MAP	High MAP	Low MAP	High MAP
-60	10 [9-12]	11 [10,11]	1.5 [1.5-1.5]	1.0 [0.9-1.0]	78 [77-79]	79 [74-83]	4.4 [4.4-4.5]	4.6 [4.4-4.8]	52 [52-53]	75 [68-83]	55 [50-60]	63 [62-64]
-40	11 [10-16]	11 [10-12]	1.1 [0.9-1.3]	0.9 [0.9-0.9]	79 [71-79]	85 [82-87]	4.7 [4.6-4.7]	4.6 [4.5-4.6]	56 [55-57]	83 [75-135]	63 [48-66]	66 [66-99]
-20	12 [11,12]	14 [12-16]	0.9 [0.8-1.0]	1.2 [0.9-1.3]	81 [80-82]	93 [84-99]	4.5 [4.4-5.1]	5.3 [4.3-6.0]	74 [49-82]	93 [87-139]	66 [57-82]	69 [69-116]
0	13 [13-18]	14 [12-16]	1.0 [0.9-1.1]	1.1 [1.0-1.2]	84 [82-108]	81 [73-96]	5.0 [4.9-5.4]	6.1 [4.9-7.1]	104 [53-115]	145 [124-192]	71 [63-80]	118 [93-143]
20	16 [14-26]	19 [13-22]	1.1 [1.0-3.3]	1.3 [0.9-1.7]	123 [120-127]	86 [78-96]	5.2 [5.2-5.3]	5.6 [5.4-6.2]	87 [80-129]	188 [178-222]	65 [53-66]	78 [60-92]
40	29 [23-36]	25 [17-34]	3.5 [3.3-4.0]	2.4 [1.3-3.6]	141 [112-148]	102 [91-107]	5.4 [5.2-5.5]	6.5 [5.9-7.4]	99 [85-120]	236 [176-294]	53 [52-55]	73 [62-97]
60	26 [20-27]	25 [24-27]	3.3 [2.9-4.7]	3.4 [3.0-3.8]	147 [146-148]	119 [117-152]	5.3 [5.2-5.7]	6.3 [5.3-6.8]	85 [73-97]	222 [195-247]	53 [50-57]	60 [49-73]
80	19 [17-19]	19 [18,19]	2.4 [2.2-2.7]	2.1 [1.7-2.2]	139 [136-142]	121 [116-151]	5.6 [5.5-6.4]	7.4 [6.7-7.5]	111 [96-147]	218 [149-280]	63 [58-69]	53 [43-75]
100	16 [15-17]	16 [16,17]	2.1 [1.8-2.3]	2.0 [1.9-2.2]	143 [135-145]	125 [103-140]	6.5 [6.3-6.8]	7.9 [7.4-8.5]	150 [145-176]	281 [136-286]	66 [62-68]	64 [56-68]
120	16 [15-20]	15 [15]	2.0 [1.6-3.4]	1.9 [1.8-2.5]	135 [130-157]	127 [126-164]	6.5 [6.1-6.9]	8.0 [7.6-8.5]	145 [101-155]	258 [135-274]	58 [56-76]	72 [63-91]
140	15 [12-15]	14 [14-16]	1.4 [1.3-2.6]	2.0 [1.6-2.6]	118 [113-153]	141 [132-170]	7.1 [7.1-7.7]	7.6 [7.4-8.6]	115 [80-173]	151 [139-155]	63 [57-75]	59 [53-71]
160	14 [14,15]	13 [12,13]	1.8 [1.3-2.1]	1.9 [1.4-2.2]	118 [112-154]	137 [137-140]	7.4 [6.7-7.7]	8.1 [7.4-9.1]	94 [77-142]	123 [121-143]	67 [61-70]	58 [53-77]
180	13 [13,14]	12 [11-13]	1.6 [1.5-1.6]	1.8 [1.5-1.8]	128 [115-130]	138 [115-146]	7.2 [6.5-7.3]	8.3 [7.5-8.9]	104 [75-106]	121 [95-144]	66 [55-72]	51 [43-82]
200	12 [12,13]	11 [10-13]	1.5 [1.3-1.5]	1.7 [1.4-1.8]	119 [112-132]	137 [114-140]	6.8 [6.5-7.3]	7.6 [6.9-8.3]	53 [41-96]	105 [94-110]	66 [58-75]	60 [56-91]

NOTE: Data are expressed as median [interquartile range]; duration of cardiopulmonary bypass (0-100 min); low MAP (40-60 mmHg); high MAP (60-80 mmHg). Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; LP, lactate-to-pyruvate ratio; MAP, mean arterial pressure.

## DISCUSSION

A technique for bedside evaluation of cerebral energy state during CPB might contribute to a reduction of neurologic complications during cardiac surgery. As the brain is dependent completely on aerobic energy metabolism, all complications threatening cerebral energy state are reflected immediately in a shift in the cytoplasmic redox state conventionally described by the LP ratio. Because of highly effective monocarboxylic acid transporters present in cell membranes, lactate and pyruvate readily pass to the extracellular interstitium.<sup>15,25,26</sup> Thus, cerebral energy state during neurocritical care is evaluated routinely from the LP ratio obtained by intracerebral MD.<sup>18</sup> In an experimental study, the authors have shown recently that during induced hemorrhagic shock, the LP ratio obtained from MD of the superior sagittal sinus reflects the simultaneously measured intracerebral LP ratio.<sup>17</sup> The present prospective, randomized, observational study was performed to test whether monitoring of the LP ratio of the venous outflow from the brain obtained by the MD technique is feasible and would reflect a shift in the global cerebral energy state during CPB. The information from the biochemical analyses were compared to that obtained from simultaneously performed bifrontal NIRS.

After the start of CPB, the mean LP ratio obtained from MD of the internal jugular vein increased significantly by 130% (high MAP) and 160% (low MAP). The 2 groups had no significant difference in venous outflow LP ratio during CPB, although low-MAP patients tended to have higher LP ratios (Fig 2A). The increase in LP ratio indicates compromised cerebral oxidative metabolism due to a decrease in cerebral blood flow, which is expected during CPB when MAP is below the normal range of cerebral autoregulation (60-160 mmHg).<sup>27,28</sup> The relation between LP<sub>Bulb</sub> ratios and the corresponding MAP (mmHg) for patients with low MAP showed a significant correlation between the 2 variables ( $R^2 = 0.46$ ;  $p=0.006$ ).

In both groups, the LP ratio returned to baseline after CPB, indicating that in the studied patients, the cerebral mitochondrial function and energy metabolism were not damaged permanently.<sup>29-31</sup> In the simultaneously performed monitoring of NIRS, no significant change in rSO<sub>2</sub> was found in either group. No significant correlation between LP ratio and rSO<sub>2</sub> was obtained (Fig 2B). This finding indicated that the monitoring LP ratio of cerebral venous blood was more sensitive to changes in cerebral oxidative metabolism than conventional NIRS measurements of rSO<sub>2</sub>. This interpretation is supported by the fact that NIRS did not detect any difference between the high- and low-MAP groups.

The increase in glycerol concentration during cerebral MD conventionally is interpreted as a result of the degradation of cellular membranes.<sup>32</sup> As the intact blood-brain barrier permeability for glycerol is limited (reflection coefficient approximately 0.48), the increase observed in jugular venous blood during CPB probably does not reflect cell membrane degradation (Table 2). Glycerol is known to be a marker of stress because augmented lipolysis releases glycerol and free fatty acids. The biochemical process is activated not only by increased sympathetic activity but also by cytokines.<sup>33</sup>

An experimental study of induced hemorrhagic shock has shown that it is possible to diagnose cerebral energy crisis from measuring LP ratio by MD of venous blood in the superior sagittal sinus.<sup>17</sup> The present study was performed to validate a similar method in humans. There were, however, several important differences between the 2 studies. First, in the experimental study,<sup>17</sup> the reduction in MAP caused irreversible cerebral damage as shown by a continuing increase in LP ratio after retransfusion of blood. In the present clinical study, the energy crisis was mild, and the energy state apparently was restored after finishing CPB (Figs 1A and 2A).

Second, in the experimental study of hemorrhagic shock,<sup>17</sup> the arterial LP ratio did not increase markedly after induction of shock. In the present study, the arterial LP ratio distinctly increased during CPB, although the difference between the LP ratio of the jugular venous blood and the arterial blood was significant in both the high-MAP group and the correlated pooled LP data (Fig 1A). During a marked decrease in MAP, an increase in LP ratio will occur in most tissues and will be reflected in the draining venous blood. However, in contrast to most other tissues, the brain is dependent exclusively on oxidative metabolism. Anaerobic energy metabolism that may be well tolerated in many organs will be deleterious for the brain. Accordingly, the significant increase in jugular LP ratio indicates compromised cerebral energy metabolism, thus validating the novel MD technique presented in this paper.

Third, during induced hemorrhagic shock, the pulmonary circulation is intact.<sup>17</sup> In the lungs, the capillary blood not only is oxygenated but the LP ratio also is equilibrated with that of the lining pulmonary cells. It is well documented that alveolar epithelial type-II cells have a rapid cellular metabolism and the potential to influence substrate availability and bioenergetics both locally in the lungs and throughout the body.<sup>34,35</sup> Accordingly, during hemorrhagic shock with intact pulmonary circulation, a normalization of the LP ratio would be expected when venous blood passes the lung. During CPB, the venous blood is oxygenated, but as the blood is not equilibrated by the metabolism of surrounding cells, the LP ratio of the venous blood would be expected to be similar to that of the arterial blood.

Intravascular MD previously has been used to monitor the lactate level of the superior vena cava during cardiac surgery.<sup>36</sup> Although the technique used was similar to that used in the present study, the information obtained and the objectives of the measurements were different. Measurement of lactate alone does not directly reflect cytoplasmic redox state or oxidative metabolism. Analysis of lactate in the superior vena cava will reflect its level in all tissues. Accordingly, the authors suggested that the technique might be useful for early lactate-guided therapy in critically ill patients.

In the present clinical study, all patients exhibited a moderate decrease in cognitive functions, as shown by a decrease in MMSE. In this small series of patients, there was no correlation to the level of MAP during CPB. Further, LP ratio rapidly returned to normal after CPB, indicating that the insult to cerebral energy metabolism was minor. However, it should be noted that the observed cognitive decline was paralleled by a significant increase in jugular venous LP ratio while no significant decline in rSO<sub>2</sub> was obtained by NIRS. The observation indicates that a larger study including high-risk patients might be indicated.

### Limitations of the Study

The sample size of this feasibility study was limited, and no sample size calculation was performed. This limited the power of the study, and the possible clinical value of the technique should be evaluated in a larger study. Future studies should include definition of normal variations in LP ratio of cerebral venous blood.

### CONCLUSIONS

The study documented that it is technically simple and feasible to place an MD catheter in the jugular bulb and monitor biochemical variables related to energy metabolism bedside. The LP ratio of cerebral venous blood increased significantly during CPB, indicating compromised cerebral oxidative metabolism, and was correlated to the decrease in MAP. In this limited number of patients, there was no significant difference between low- and high-MAP groups regarding venous outflow LP ratio during CPB, but low-MAP patients tended to have higher LP ratios. The increase in the jugular bulb LP ratio was significantly higher than the increase in LP ratio of the arterial blood. Conventional monitoring of rSO<sub>2</sub> by NIRS did not show a corresponding decrease in cerebral oxygenation. As the patients exhibited decreased cognitive functions after CPB, an increase in jugular venous LP ratio may be a sensitive indicator of impending cerebral damage.

The possible clinical value of the technique should be evaluated in a larger study. Future studies should include definition of normal variations in LP ratio of cerebral venous blood and the relation between the increase in LP ratio and the development of permanent cognitive deterioration and neurologic lesions.

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