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

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***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 ($LP_{arterial}$ 17 [15–20] *v* $LP_{venous}$ 26 [23–27]; p = 0.0001). No cerebral desaturations (decrease in $rSO_2 > 20\%$ from baseline) were observed in either group during CPB. In each group, 50% of the patients showed significant cognitive decline (mini-mental 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 $rSO_2$ 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.**



***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.[1,2] Recent studies report post–coronary artery bypass grafting (CABG) stroke rates of 1% to 5%.[3] 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.[4] A number of pathophysiologic processes underlie the neurologic complications, which necessitate a multifaceted therapeutic approach.[2,5] 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.[6–9] 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.[10] 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 ($rSO_2$). 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 $rSO_2$ was shown to be associated with fewer incidences of major organ dysfunction.[11,12] However, in a large systematic review, it was concluded that only low-level evidence linked low $rSO_2$ during cardiac surgery to postoperative neurologic complications.[13]

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.[14] Due to monocarboxylic acid transporters, lactate and pyruvate readily pass cellular membranes.[15] The change in cytoplasmic LP ratio is detected immediately by interstitial MD.[16] 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.[17] 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.[18,19] 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 μM, 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 μg) 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, $PaO_2$ was maintained at 17.0-to-22.0 kPa, $PaCO_2$ 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 Stökert 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°C using a Sorin cardioplegia heat exchanger CSC14. A triple-transducer set, DTX Plus (Argon), was used for preoxygenator, postoxygenator, 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 (metaoxidrine, norepinephrine $<0.30$ μg/kg/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/$m^2$ and was maintained at the same level unless SvO2 declined below 65%. The temperature target was 37.0°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 $rSO_2$ values were recorded simultaneously preoperatively and intraoperatively and for 2 hours postoperatively. Cerebral desaturation was defined as a decrease in the relative $rSO_2$ value of 20% compared with the individual preinduction baseline value.[13] 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.[20]

The MD catheters were perfused by MD pumps (106, MDialysis AB) at 0.3 μL/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.[21] 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.[22] 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.[22,23] 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.[24]