Disturbance in Venous Outflow From the Cerebral Circulation Intensifies the Release of Blood-Brain Barrier Injury Biomarkers in Patients Undergoing Cardiac Surgery

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Objective: **Disturbances in venous outflow from the cerebral circulation may result in brain injury. Severe increases in brain venous pressure lead to brain ischemia and, subsequently, brain edema and intracranial hemorrhages.**

The purpose of this study was to determine the effect of changes in jugular venous bulb pressure (JVBP) on plasma blood brain-barrier biomarkers concentration and disturbances in arteriovenous total and ionized magnesium ($_{a\text{-}v}$tMg and $_{a\text{-}v}$iMg) in brain circulation in patients undergoing coronary artery bypass grafting surgery (CABG) with cardiopulmonary bypass (CPB).

Design: **Prospective observational study.**

Setting: **Department of Cardiac Surgery at a Medical University Hospital.**

Participants: **Ninety-two adult patients undergoing elective CABG with CPB under general anaesthesia were studied.**

Methods: **Central venous pressure (CVP) was measured using a pulmonary artery catheter. The right jugular vein was cannulized retrogradely for jugular venous bulb pressure (JVBP) measurement. Concentrations of plasma S100β protein, matrix metalloproteinase 9 (MMP-9), creatine kinase isoenzyme BB (CK-BB) $_{a\text{-}v}$tMg and $_{a\text{-}v}$iMg were measured as the markers of blood-brain barrier dysfunction. All of them were analyzed in comparison with JVBP during surgery and the early postoperative period.**

Results: **Elevated JVBP was noted after CPB and after surgery. Its increase above 12 mmHg intensified release of S100β, MMP-9 and CK-BB as well as disorders in $_{a\text{-}v}$tMg and $_{a\text{-}v}$iMg. CVP correlated with JVBP, S100β, and MMP-9. Moreover, JVBP correlated with S100β and MMP-9.**

Conclusions: **Cardiac surgery increased JVBP, and JVBP elevated above 12 mmHg intensified an increase in biomarkers of plasma blood-brain barrier disruption.**

KEY WORDS: ***cerebral circulation, blood-brain barrier, neurologic injury, cardiac surgery, cardiopulmonary bypass, brain venous pressure, S100β protein, matrix metalloproteinase 9, creatine kinase***

PERIOPERATIVE DISTURBANCES in cerebral circulation are one of the main ethologic factors of postoperative neuropsychological disorders in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[1–3] Significant decrease in cerebral blood flow may disturb brain metabolism leading to neuronal and glial injury and raised blood-brain barrier (BBB) permeability.[4,5] Moreover, some authors documented a strong correlation between perioperative disorders in cerebral circulation and occurrence of stroke in cardiac surgery patients.[6] Unfortunately, a majority of studies describe arterial disturbances in cerebral blood flow and the effect of disorders in venous outflow from brain circulation has been documented poorly in cardiac surgery patients.

Multiple data present brain injury following severe disturbances in venous outflow from brain circulation.[7–14] A reduction in venous outflow increases dural sinus pressure, decreasing venous outflow and leading to cerebral venous hypertension.[7,13,14] Elevated cerebral venous pressure subsequently decreases cerebral blood flow, increases intracranial pressure (ICP) leading to pressure-dependent BBB disruption.[7,8,14,15] Moreover, an increase in cerebral venous pressure elevates cerebrospinal fluid (CSF) pressure and volume and may enlarge brain volume.[16] Brain ischemic events, brain infarct, and venous hemorrhage are endpoints of elevated cerebral venous pressure. They occur approximately in 10% to 75% of patients with cerebral venous hypertension.[7,9,10,17]

Disorders in venous outflow from the brain circulation may disturb BBB permeability. An increase in the jugular vein pressure decreases venous outflow from brain circulation, increasing fluid leakage into the perivascular space, which leads to parenchymal edema and then massive brain edema and/or hemorrhage.[7,8] Some experimental data documented a significant decrease in brain oxygenation measured by near-infrared spectroscopy (NISR) following decline in venous outflow in pigs undergoing CPB.[11,12] Recently, the authors found a strong correlation between blood saturation in the jugular vein bulb (SjO_2) and jugular vein bulb pressure (JVBP), particularly in patients with JVBP higher than 12 mmHg.[18] Moreover, the authors documented a significantly higher increase in plasma glial and neuronal injury biomarkers, such as glial fibrillary acidic protein (GFAP) and tau protein, and higher brain metabolic disorders in patients with elevated JVBP above 12 mmHg. Based on previous observation, it was assumed that the increase in JVBP may also intensify disturbance in BBB permeability and release characteristic for BBB dysfunction neurobiomarkers such as S100β protein, matrix metalloproteinase 9 (MMP-9), the brain type creatine kinase isoenzyme BB (CK-BB) and arteriovenous total and ionized magnesium concentrations ($_{a\text{-}v}$tMg and $_{a\text{-}v}$iMg, respectively).

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S100β protein in a low molecular weight is a binding protein that is found predominantly in astroglial and Schwann cells.[19] Physiologically, plasma S100β concentration is below 0.2 μg/L, and its increase above 0.5 μg/L is considered as pathologic.[19,20] An increase in S100β has been observed immediately after traumatic or nontraumatic BBB disruption following raised synthesis and release from an injury's activated glia.[20,21] Matrix metalloproteinases 9 is a zinc-dependent endopeptidase that plays a crucial role in neuro-inflammation.[22] Physiologically, its plasma concentrations range from 15 to 100 ng/mL.[22,23] The active MMP-9 increases the BBB permeability degrading the extracellular matrix, basal lamina and junctions between endothelial cells.[22,24] Therefore, the plasma MMP-9 concentration is considered to be a sensitive marker of brain edema. CK-BB plays a crucial role in the cellular metabolism in neurons. Several studies presented its elevation following brain injury.[25,26] Normally, CK-BB is not detectable in plasma and its presence documents BBB injury.[25]

The aim of the present study was to analyze the effect of increasing JVBP on plasma S100β protein, MMP-9, CK-BB and $_{a\text{-}v}$tMg and $_{a\text{-}v}$iMg in patients undergoing elective coronary artery bypass grafting surgery (CABG) with CPB.

PATIENTS AND METHODS

The study methodology was described previously.[18,27,28] The study design was approved by the Committee for Bioethics of the Medical University at Lublin, and written informed consent was obtained from all patients. Patients scheduled for elective CABG with CPB due to stable angina pectoris were included. Patients with current neurologic disease or history of neurologic disorders after brain surgery, severe head trauma, significant carotid artery stenosis, chronic respiratory disease, serious endocrine disease, chronic renal insufficiency, unstable angina pectoris, chronic renal failure, or the EuroScore higher than 8 were excluded.

One day prior to surgery, all patients received 2 mg of lorazepam (Lorafen, Polfa, Poland). Moreover, 1 hour before the induction of anesthesia, they received intramuscular midazolam (Sopodorm, Polfa, Poland) with morphine (Morphicum hydrochloricum, Polfa, Poland), at 0.01 mg/kg and 0.1 mg/kg, respectively. General anesthesia was induced using 0.01 to 0.02 μg/kg of fentanyl (Fentanyl, Polfa, Poland), 0.05 to 0.1 mg/kg of midazolam, and 0.1 to 0.5 mg/kg of etomidate (Etomidate, Braun, Germany). Muscle relaxation was obtained with a single dose of pancuronium (Pavulon, Jelfa, Poland) (0.08-0.1 mg/kg). All patients were ventilated using intermittent positive-pressure ventilation (IPPV) with a mixture of air and oxygen (F_IO_2-0.4) with the tidal volume (5-7 mL/kg body weight), respiratory rate (9-12 per min), peak inspiratory pressure (P_{Peak}) not higher than 30 cmH_2O, and positive end-expiratory pressure (PEEP) 2-3 cmH_2O. Parameters were adjusted to maintain normocapnia ($PaCO_2$ ranges between 35-45 mmHg), which was controlled by repeated blood gas analysis. Anesthesia was maintained throughout the procedure using a midazolam-fentanyl infusion. Additionally, prior to initiating CPB, some patients received the volatile anesthetic isoflurane (Forane, Baxter International Inc, Deerfield, IL) or sevoflurane (Sevorane, Abbott, GB) at a dose of 0.5 MAC. The sealed envelope method was used to determine the kind of volatile anesthetic used. The dose of anesthetic administered was dependent on the patient's hemodynamic status. Intraoperative hypertension was treated with a single bolus of a midazolam-fentanyl mixture. In patients responding inadequately to anesthesia, a single intravenous dose of urapidil was used (Ebrantil, Altana, D). Tachycardia was treated with beta-blockers.

The left jugular vein was cannulated using a 3-lumen cannula (ARROW, USA). Additionally, a pulmonary artery catheter (ARROW, USA) was inserted via the left internal jugular vein. Next, the right jugular vein was cannulated retrogradely for continuous jugular bulb venous pressure (JBVP) measurement. The placement of all cannula was confirmed by x-ray. Pulmonary and systemic hemodynamic parameters were measured during the surgery and in the early postoperative period.

Prior to CPB, heparin (Heparin, Polfa, Poland) was administered at a dose of 300 IU/kg and the activated coagulation time was controlled up to 400 seconds. For CPB, standard cannulation of the ascending aorta and dual-stage venous cannulation through the right atrium were performed. During mild hypothermic CPB ($>34^\circ$ C), circulation and ventilation were maintained with the heart-lung machine S III (Stöckert, Germany), and the mean arterial pressure was kept between 45 and 105 mmHg. After traditional aortic clamping, myocardial viability was preserved with repeated antegrade hyperkalemic warm blood cardioplegia. Rewarming was carried out with fewer than 10 degrees gradient difference between venous blood and water temperature until the temperature reached 37° C in the esophagus. Distal anastomoses were performed during cardioplegic arrest, whereas proximal anastomoses were performed with resumed perfusion on a side-biting clamp. Mediastinal blood was aspirated into the cardiotomy reservoir of the heart-lung machine. The last suction was just before decannulation. The residual blood from the CPB circuit was retransfused intravenously. In all cases, separation from the heart-lung machine was uneventful, and intra-aortic counterpulsation was not necessary. In patients requiring inotropic support, dopamine or dobutamine infusions were used at doses dependent on the patient's hemodynamic status. The effect of heparin was reversed by an adequate dose of protamine sulphate (Protaminum sulphuricum, Biomed, Poland).

After surgery, patients were sent to the postoperative intensive care unit (PICU). All were extubated 8 to 12 hours after surgery and were transferred from the PICU between the second or third postoperative day.

Blood samples were collected from the radial artery for S100β protein, MMP-9, CK-BB, and arterial tMg and iMg measurements. Venous tMg and iMg were measured in samples collected from the jugular bulb vein. The jugular bulb venous pressure was measured continuously and was considered as cerebral venous pressure. All biochemical parameters were measured at 5 time points: (1) after the induction of anesthesia and prior to surgery, (2) 10 minutes after disconnection of the heart-lung machine (after CPB), (3) after completion of the procedure but before the patient's transfer to the postoperative intensive care unit, (4) the morning of the first postoperative day and (5) the morning of the second postoperative day.

Based on previous assumptions,[18] all participants were divided into group N with normal JVBP (lower than 12 mmHg) and group H with pathologic JVBP (higher than 12 mmHg) during surgery and the early postoperative period. (The pathologic level of JVBP was assumed based on changes in plasma GFAP and lactate concentrations and SjO_2. The increase in GFAP above 0.49 ng/mL, absolute value of arterio-venous lactate above 0.2 mmol/L and decrease SjO_2 below 55% for JVBP.)[18]

The blood samples were collected from the radial artery and immediately centrifuged (2,500 r/min); the serum obtained was frozen at -20° C. The immunoassay methods were used for S100β measurements. All probes were defrosted and centrifuged again (50,000 r/min). Next, 2 monoclonal mouse antibodies (anti-S100β conjugated with HRP, BSA and 0.5% ProClin) were used for β-chain detection (Sangtec® S100β ELISA, Biokom – DiaSorin, Avenue, USA).

The enzyme-linked immunosorbent assay (ELISA) method was used to determine serum active MMP-9 concentrations. The defrosted