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# Relationship between cerebral injury and inflammatory responses in patients undergoing cardiac surgery with cardiopulmonary bypass

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**Abstract**

This study was performed to evaluate whether cytokines, adhesion molecules, ghrelin and S-100B are useful markers in predicting the cerebral infarction after cardiac surgery with cardioplumomary bypass (CPB). The patients ($n = 20$) were classified into two groups; group A ($n = 4$) showed postoperative organized cerebral damage, while group B ($n = 16$) consisted of patients without occurrence of postoperative strokes. Before CPB, serum levels of S-100B in both groups A and B were low (<0.5 ng/mL), while ghrelin concentrations in group A (all patients had history of strokes) were much higher than those in group B. After CPB, when serum levels of S-100B in group A at 24 h were higher than those in group B, ghrelin in group A at same time point showed high levels in comparison to group B. At 12 and 24 h after CPB, levels of tumor necrosis factor (TNF)-α, interleukin-10 and soluble TNF-receptor I in group A were significantly higher than those in group B. In conclusion, it is considered that ghrelin as well as S-100B can be a useful marker for the prediction of stoke after CPB. Increase of TNF-α, interleukin-10 and soluble TNF-receptor I after CPB may be involved in the pathogenesis of stroke after CPB.


*Keywords:* Cytokines; S-100B; Adhesion molecules; Ghrelin; Cardioplumomary bypass

## 1. Introduction

Cerebral injury is a devastating complication that can occur in cardiac surgery with cardiopulmonary bypass (CPB) and often results in patients being unable to enjoy the original benefits of the operation. Diagnosis of cerebral injury has depended on clinical neurological tests, cranial computed tomography (CT) or magnetic resonance imaging. However, these methods may not be available for patients soon after cardiac surgery, as patients may be unconscious, sedated, or treated by ventilator. The certification of biochemical serum markers to support the diagnosis of cerebral injury would potentially be useful.

S-100 protein, a member of a family of calcium-binding proteins, is considered to be a beneficial marker for the prediction of cerebral infarction in patients who

*Abbreviations:* CPB, cardioplumomary bypass; TNF, tumor necrosis factor; IL, interleukin; CT, computed tomography; CNS, central nervous system; sTNF, soluble TNF; sP-selectin, soluble P-selectin; sE-selectin, soluble E-selectin; GH, growth hormone; TAT, thrombin–antithrombin III complex; FDP, fibrinogen degradation products; hCRP, high-sensitivity c-reactive protein; AAG, α1-acid glycoprotein; AAT, α1-antitrypsin.

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have had a stroke following cardiac surgery, because it leaks from damaged nerve cells into cerebrospinal fluid and appears in the serum only if there is also an increased permeability in the blood–brain barrier [1–3]. S-100 protein has three dimeric isoforms, S-100a0, S-100a and S-100B, which are formed by αα, αβ and ββ subunits, respectively [4–6]. S-100B (S-100 ββ) is found predominantly in glial and Schwann cells, as well as in neurons [7]. We have previously reported that serial measurement of serum S-100B in the initial 12 h after CPB can be used to predict early postoperative brain injury [8].

On the other hand, it has been indicated that inflammatory–immunologic reactions are involved in the pathogenesis of cerebral ischemia [9]. Inflammatory cells such as neutrophils and macrophages have been shown to infiltrate into the ischemic brain in various experimental animals suffering form ischemic stroke and in patients with cerebral ischemia [9–12]. Inherent cells, such as astrocytes, microglia and endothelia, have been found to be activated by cerebral injuries including ischemic stroke. These cells become immunologically reactive and interact with substances including cytokines and adhesion molecules. Inflammatory responses play an important role in the pathogenesis of cerebral lesions following stroke, and in the early stages of stroke leukocytes infiltrate into the ischemic region and cause brain edema [13]. In our experience, patients with arteriosclerosis in the internal carotid artery occasionally cause the rupture of unstable plaques during operations. These data suggest that arteriosclerosis in the carotid artery and rupture of unstable plaques may be the risk factors involved in the occurrence of cerebral injury during or after CPB.

After stimulation by lipopolysaccharide and interleukin (IL)-1β, cells of the central nervous system (CNS) can express various cytokines and adhesion molecules [14,15]. Several experimental data have shown that tumor necrosis factor (TNF)-α, which is a pro-inflammatory cytokine, appears to be involved in the blood–brain barrier, inflammatory, thrombogenic, and vascular changes associated with brain injury [9]. TNF-α levels in brain tissue, cerebrospinal fluid, and plasma have been found to be elevated in several CNS disorders [10,16]. Two distinct TNF receptor subtypes are present in many cell types and mediate biological activities of TNF-α [17]. Soluble forms of these receptors are produced by proteolytic cleavage of the extracellular domains of membrane-bound TNF receptors, and exist in the blood. The soluble TNF receptors have molecular weights of 55 kDa (sTNF-RI) and 75 kDa (sTNF-RII), and are found in human serum. The soluble receptors may regulate the bioactivity of TNF-α [18]. Plasma concentrations of sTNF-RI and sTNF-RII are increased by inflammatory stimuli such as TNF-α, and they remain elevated in circulation much longer than TNF-α [19]. However, the changes in the levels of the two receptors in patients with acute cerebral ischemia are not clear [20]. IL-6 is also a pro-inflammatory cytokine and associated with the development of complications in patients undergoing cardiac surgery with CPB [21]. IL-10 is a potent anti-inflammatory cytokine and inhibits the production of pro-inflammatory cytokines including TNF-α [22]. Experimentally IL-10 has been found to limit development of ischemic damage, but there is no precise evidence of its relationship with heart function in humans [23].

Increased concentrations of soluble adhesion molecules may serve as markers for activated or damaged endothelium [24]. P-selectin is stored in the platelets' α granules and endothelial Weibel–Palade bodies and, upon activation of these cells, is translocated to the cell surface and excreted into circulation as a soluble form (sP-selectin) [25]. Several studies have demonstrated that high concentrations of sP-selectin are associated with increased morbidity and mortality in diseases characterized by microcirculatory disorders involving activated endothelium, platelets and leukocytes [26–28]. E-selectin is expressed on activated microvascular endothelium, and is involved in the adherence pathway of neutrophils to the endothelium [29]. This selectin is secreted maximally 2–4 h after cell activation and then is rapidly eliminated from the cell membrane by proteolytic shedding into circulation [30]. Increases of serum concentration of P-selectin and E-selectin in patients after cardiopulmonary resuscitation have also been reported [31].

Ghrelin, an amino acid peptide, is the endogenous ligand for the growth hormone (GH) secretagogue receptor [32]. Ghrelin is secreted mainly by stomach, though it is also produced in small amounts by pancreas, hypothalamus, and other organs [32,33]. Ghrelin antagonizes leptin through the activation of the hypothalamic neuropeptide Y/Y1 receptor pathway [34]. In rheumatoid arthritis (RA), ghrelin plasma levels decrease when compared with healthy controls [35]. In contrast, plasma levels of ghrelin increased in cachectic patients with chronic heart failure, and this phenomenon is associated with increases in GH and TNF-α [36].

In the present study, to investigate whether the induction of cytokines and adhesion molecules in the early stage of stroke play a critical role in the pathogenesis of cerebral infarction after cardiac surgery with CPB, we measured patients' circulating levels of cytokines, cytokine receptors, inflammatory markers and soluble adhesion molecules at various times after CPB. Furthermore, to investigate the relation between cerebral dysfunction and intraoperative thromboembolism, we measured thrombin–antithrombin III complex (TAT) as coagulation-related factor and fibrin and fibrinogen degradation products (FDP) as fibrinolysis-related