Review

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S100B in cardiac surgery brain monitoring: friend or foe?

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Abstract: Recent advances in perioperative management of adult and pediatric patients requiring open heart surgery (OHS) and cardiopulmonary bypass (CPB) for cardiac and/or congenital heart diseases repair allowed a significant reduction in the mortality rate. Conversely morbidity rate pattern has a flat trend. Perioperative period is crucial since OHS and CPB are widely accepted as a deliberate hypoxic-ischemic reperfusion damage representing the cost to pay at a time when standard of care monitoring procedures can be silent or unavailable. In this respect, the measurement of neuro-biomarkers (NB), able to detect at early stage perioperative brain damage could be especially useful. In the last decade, among a series of NB, S100B protein has been investigated. After the first promising results, supporting the usefulness of the protein as predictor of short/long term adverse neurological outcome, the protein has been progressively abandoned due to a series of limitations. In the present review we offer an up-dated overview of the main S100B *pros* and *cons* in the perioperative monitoring of adult and pediatric patients.

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Introduction

Congenital heart diseases (CHD) are a heterogeneous entity characterized by anatomic malformations of the heart and/or great arteries occurring during intrauterine development [1, 2]. CHD comprise 28% of all major congenital anomalies and the incidence is estimated at 8–9 per 1,000 live births per year [3]. Given a worldwide annual birth rate of around 150 million, this means that each year 1.3 million infants are born with CHD [1–4]. Approximately 30% of neonates born with CHD are critical and need surgical correction within the first year of life to avoid early death. Neurocognitive developmental damage is present in 50% of the survivors [1–5].

In the last few decades, open heart surgery (OHS) by means of cardiopulmonary by-pass (CPB) has raised survival incidence from 67% (1979–1993) to 89% (1994–2005) [6]. Conversely, perioperative and long-term morbidity have increased, especially for complex CHD [6]. At this stage, the keyword for health care systems is "reducing morbidity". Among main standard interventions, prenatal ultrasound screening (PUS) for early CHD diagnosis is the preferred option in developed countries: in non-cyanotic CHD, PUS can improve the success of fetal cardiac interventions and can guarantee appropriate preparation for delivery and the post-neonatal period. However, the rate of abortion as a last resort for complex CHD management is still increasing [7, 8].

The quality of perioperative monitoring both in children and adults is crucial in order to promptly detect cases at risk of OHS complications, thus preventing or minimizing neurological damage. Today, despite accurate perioperative longitudinal neuro-monitoring by means of electroencephalography (EEG) or amplitude-integrated electroencephalography (aEEG), transcranial Doppler (TCD) and near-infrared

spectroscopy (NIRS), brain damage can occur at a stage when standard procedures may be silent or unavailable [9–15]. Thus, the inclusion in daily clinical practice of new tools such as neuro-biomarkers (NB), able to provide useful information about well-being/stress on the central nervous system (CNS) during OHS, are eagerly awaited. In this light and especially in infants and children, the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the National Institutes of Health (NIH) have recently established a series of criteria which must be met for NB inclusion in clinical practice [16–18]. In adults, newer and more useful neuromonitoring strategies in OHS are still of great interest for the improvement of quality of life [19]. Literature data reported that the monitoring of S100B protein in non-CHD infants and traumatic brain injured children has already been included in daily clinical practice [20, 21]. However, no consensus has been found on the usefulness of the protein in CNS perioperative monitoring of CHD population and of adult patients.

Therefore, the purpose of the present review is to investigate the *pros* and *cons* of S100B protein assessment in the perioperative period of CHD infants and adult OHS population.

Research strategy

The literature review was performed by conducting electronic searches of MEDLINE (via PubMed and PubMed Central), EMBASE, CINHAL and the Cochrane Library. The electronic search used the following keywords and MeSH terms: (i) congenital heart diseases AND (S100 OR S100beta OR S100 protein OR S100B OR biomarkers of cerebral damage); (ii) cardiac surgery AND (S100 OR S100beta OR S100 protein OR S100B OR biomarkers of cerebral damage); (iii) cardiopulmonary bypass AND (S100 OR S100beta OR S100 protein OR S100B OR biomarkers of cerebral damage); (iv) brain monitoring in cardiac surgery AND (S100 OR S100beta OR S100 protein OR S100B OR biomarkers of cerebral damage); (v) neurological damage in cardiac surgery AND (S100 OR S100beta OR S100 protein OR S100B OR biomarkers of cerebral damage). No publication date limits were set. To enable full understanding of the studies, the inclusion criteria were: (i) primary (original) research published in a peer-reviewed journal in the English language and (ii) full text available. For the same reason, case reports, commentaries, letters to the editor, and reviews were excluded. Articles including data related to animal models were also excluded. Literature searches were performed in the period between 1 January 2019 and 1 November 2020.

Cardiopulmonary by-pass

The performance of CPB in adults and CHD infants varies according to the complexity of the disease. In adult patients, CPB is performed in the majority of cardiac surgery procedures including coronary artery bypass grafting, valvular repair/replacement, complex CHD repair [22]. In infants, data reported that the incidence of CPB has increased dramatically, especially for cyanotic CHD repair [6]. The primary objective of OHS-CPB is to guarantee cardiac output and multi-organ oxygenation maintaining a more stable cerebral blood flow throughout surgery. Although such perioperative management decreased neurological morbidity, brain damage still remains a major post-operative complication both in adults and in children [23–32]. Intraoperative interventions (CPB and circulatory arrest techniques), inadvertent events from surgical procedures (thromboembolic events, strokes, intracranial hemorrhage), and uncorrectable hypoxia/cyanosis in the post-operative period are considered the main responsible factors in neurodevelopmental outcomes in these patients [19, 23–27, 32]. Moreover, brain injury enhancing factors such as hyperthermia, hyperglycemia and systemic inflammatory response during the perioperative period also contribute to the development of such complications [33].

The mechanisms underlying the development of brain injury during and after cardiac surgery is mainly due to hypoxic-ischemic (HI) insult, followed by the reperfusion phase and more recently the so-called “third phase”, which continues for weeks and months after the primary insult [34]. Soon after HI insult, primary energy failure occurs with deprivation of the glucose and oxygen supply resulting in a switch to anaerobic metabolism and deleterious effects on vascular autoregulation. The advancing of HI injury actives a biochemical cascade leading to cellular injury [34–40]. Secondary energy failure occurrence varies according to insult characteristics with onset at about 8–16 h and a nadir at about 24–48 h. Finally, gliosis, persistent inflammatory receptor activation and epigenetic changes are responsible for the tertiary phase (Figure 1) [35–43].

CPB and neurological pattern in adults

In adults, short (memory and visuospatial ability loss) and long-term (ischemic stroke, cognitive decline) neurocognitive impairment are commonly encountered after OHS and CPB [43–46]. Minute fatty micro-emboli constitute the major source of post-OHS neurological dysfunction

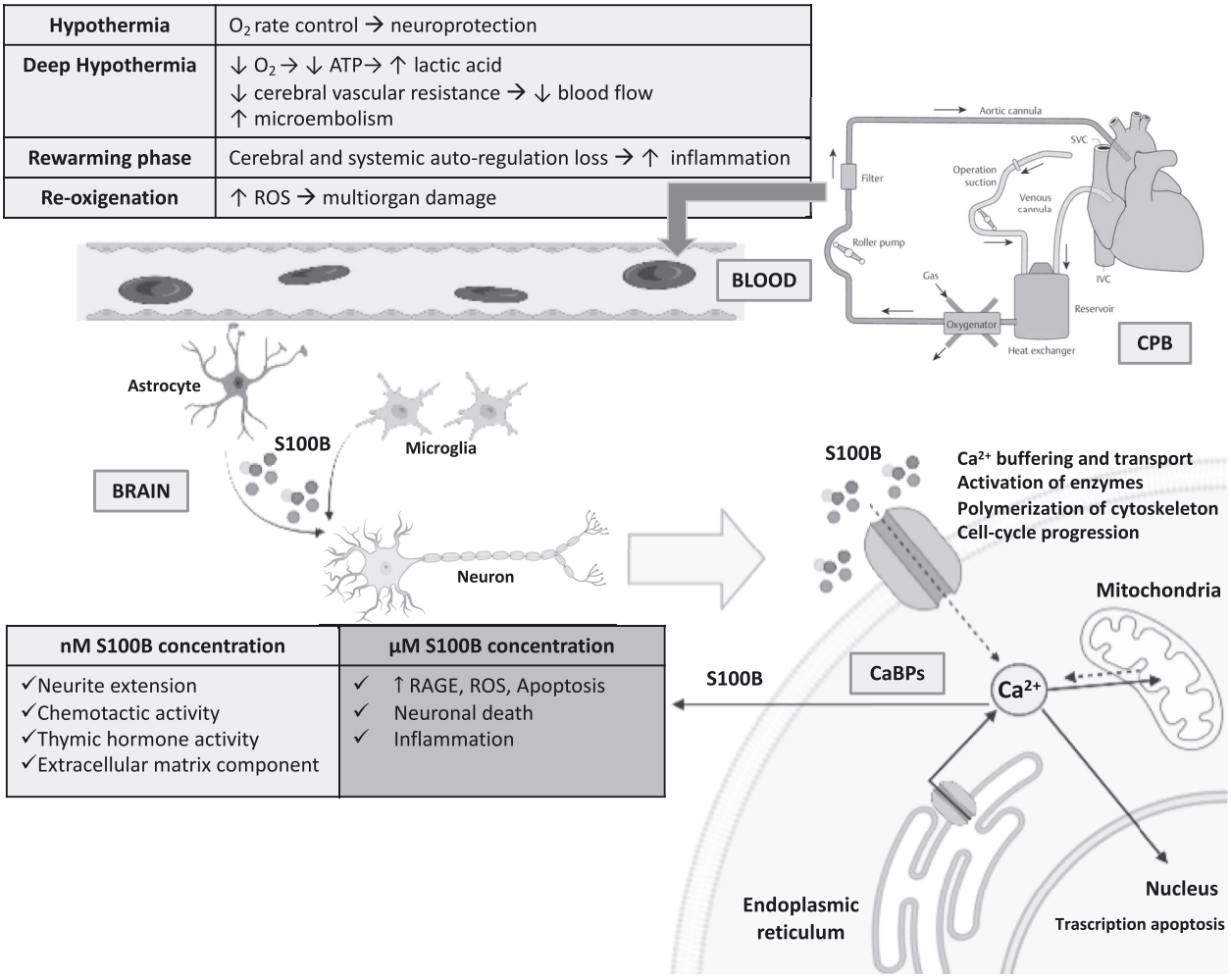

Figure 1: Biochemical cascade of events involving S100B protein in patients undergone to open heart surgery and cardiopulmonary bypass. O_2, oxygen; ATP, adenosine triphosphate; ROS, reactive oxygen species; SVC, superior vena cava; IVC, inferior vena cava; CPB, cardiopulmonary bypass; Ca^{2+}, calcium; nM, nanomolar; µM, micromolar; CaBPs, Ca^{2+}-binding proteins; RAGE, receptor for advanced glycation end products.

where cerebral hypoperfusion and systemic inflammation play a role either as primary offenders or exacerbating factors. Other explanations regard CPB strategy (pH-stat, α-stat), duration, and hypothermia/rewarming degree and speed. In addition, non-pulsatile flow, hemodilution, pressure autoregulation, anesthetic/cerebro-protective drugs, and the neuroimmune response to CPB can alter cerebral perfusion and metabolism [43–46].

The persistence of post-operative neurocognitive changes may be partially due to patient-specific risk factors rather than OHS-CPB procedures. This holds for stroke post-OHS incidence (about 1.2–5.7%), which seems to be directly age-related, increasing every decade, and often associated with a medical history comprising the cardiovascular, kidney, respiratory and metabolic systems [46].

CPB and neurological pattern in infants

CHD are at high risk of intrauterine, neonatal and/or superimposed perioperative HI, contributing to global CNS dysmaturation [34, 36–42, 47]. Long-term neurocognitive and motor impairments are commonly diagnosed in the survivors, including poor impulse control, attention deficit, hyperactivity, mild language and cognitive deficit, and limited executive functioning ability. Although appearing outwardly normal, children with such deficits have poor academic performance and a lack of adult employability. They may also suffer high rates of depression and poor quality of life [48].

The issue that CNS damage due to OHS and CPB is mostly neither thrombotic nor hemorrhagic suggests that

optimizing the hemodynamic parameters during CPB could significantly reduce the incidence of neurological deficits [49, 50]. Apart from non-modifiable characteristics such as cardiac diagnosis, genetic anomalies, birthweight, prematurity, brain immaturity and gender [1–5], many other intra-operative-related temperature and flow-dependent factors potentially play a role in the development of neurological damage in infants. Among these, deep hypothermia circulatory arrest (DHCA), hypoperfusion, air emboli and systemic inflammatory response are the main causes [28, 30, 31, 50–64].

Altogether, it is possible to argue that there are significant differences in CPB management as well as in post-OHS CNS clinical patterns. The main ones regard the need in infants/children for extreme measures which are unnecessary in adults, such as DHCA, hemodilution, acid-base strategies, low perfusion pressures and wide variation of perfusion flow rates (Table 1). Nonetheless, smaller circulating blood volume, higher oxygen consumption rate, reactive pulmonary vascular bed, immature organ systems, and altered thermoregulation constitute differentiating factors explaining the different vulnerability to deleterious OHS-CPB effects in infants/children [50] (Table 1).

CPB neuromonitoring

The main target of the monitoring strategy is to reach and maintain an adequate cerebral perfusion during cardiovascular surgery, thereby preventing or minimizing neurological damage. Today, the most applied non-invasive neuromonitoring strategies include electroencephalography EEG or aEEG, TCD and NIRS [9–15, 65].

Table 1: Cardiopulmonary by-pass management comparison between adult and pediatric patients.

Parameter	Adult	Pediatric
Minimum CPB temperature, °C	25–32	15–25
DHCA	Rare	Frequent
Pump prime		
Blood volume dilution, %	25–33	100–300
Whole blood or RBC support	Rare	Frequent
Perfusion pressure, mmHg	50–80	20–50
Acid-base management strategy	α-stat	pH-stat
Temperature, °C	>28–30	<28–30
Glucose management		
Hyperglycemia requiring insulin therapy	Frequent	Rare
Hypoglycemia	Rare	Frequent

CPB, cardiopulmonary by-pass; °C, celsius; DHCA, deep hypothermic circulatory arrest; RBC, red blood cells; Y, yes; N, no.

EEG or aEEG

Pros

EEG/aEEG provide useful information on large electrocortical activity areas, detecting subclinical seizures and confirming electrical silence during deep hypothermia [9, 10].

Cons

EEG/aEEG suffer from low resolution and cannot easily detect smaller areas of cortical ischemia. Hypothermia/DHCA and related therapeutic strategies such as anesthesia are the main bias for EEG/aEEG interpretation and experienced personnel are required [19].

TCD

Pros

TCD allows continuous and bilateral recordings of cerebral blood flow velocities through the major cerebral vessels during OHS-CPB phases. Decreased blood flow velocities in cerebral vessels have been associated with poor cognitive performance [11, 65] as well as high-intensity transient signals (HITS) which appear on the spectral envelope display to indicate an embolic event.

Cons

TCD monitoring requires an experienced team in order to limit several side-effects, such as HITS artifacts and the impossibility of differentiating gaseous from particulate emboli. In addition, other intra-operative issues such as constant probe position and sterile environment maintenance are limitations deserving consideration [19].

NIRS

Pros

NIRS provides non-invasive longitudinal monitoring of cerebral oximetry, function and hemodynamics. It detects hypoxia-ischemia insult during CPB associated CNS injury and later neurodevelopment [12–15, 66–68].

Cons

NIRS suffers from signal contamination from extracranial tissues and significant intra-patient and inter-patient

variability in baseline regional cerebral oxygen saturation ($rcSO_2$) levels. Main limitations regard changes in the partial pressure of CO_2 affecting the distribution of arterial and venous blood in the cranial vault, hemodilution, tissue edema, and skin pigmentation that may impact $rcSO_2$ availability. Additional factors are related CPB-phases such as cooling/rewarming, DHCA and CPB duration [19].

Finally, on the basis of the aforementioned findings it is reasonable to argue that despite recent technological advances in neuromonitoring of patients who have undergone OHS-CPB, the possibility of detecting perioperative brain injury is an issue needing much further study.

Biochemical markers

The assessment of NB in biological fluids may provide an alternative, direct indicator of cell damage in the CNS when clinical, laboratory and radiological standard monitoring parameters are silent or unresponsive. They have the advantage of providing a quantitative indicator of the extent of brain lesions. More recently, FDA, EMA and NIH have voiced support for NB research. They encourage the integration of NB in drug development and their appropriate use in clinical practice by promoting NB qualification programs [16–18]. For example, in adults, as part of this process, new methods of assessing β-amyloid 1–42 and t-tau in the cerebrospinal fluid (CSF) of Alzheimer patients and of amyloid imaging using positron emission tomography have already been validated [69, 70]. Indeed, circulating cardiac Troponins T-I have been included in clinical guidelines as markers of cardiac morphologic damage [71] as well as glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 in traumatic brain injury [72, 73].

In the perinatal period, the statements required by official institutions for validation of a NB in clinical guidelines are completely different than at adult age. In this regard, an optimality score for a NB has been defined that includes several criteria that need to be met as far as possible. In particular, the optimal NB should be: 1. alternative and direct indicator of CNS damage when clinical and radiological assessments are still silent; 2. early predictor of degree and location of injury; 3. indicator of the extent of brain lesion; 4. marker of disease progression; 5. well-studied in the pediatric population; 6. measurable worldwide by commercially available and easily reproducible kits; 7. with an available range of reference for the pediatric population; 8. ability to be assessed in different biological fluids (CSF, blood, amniotic fluid, urine, saliva, milk) [18, 36, 41, 74–79].

Over the last few decades, NB such as oxidative stress markers, neuro and calcium binding proteins, inflammation biomarkers and vasoactive agents were evaluated as tools for prognostic evaluation in non-CHD/CHD infants and in the adult population [18, 36, 72–79].

Adenylate kinase, creatinine phosphokinase isoenzyme BB, lactate, myelin basic protein, S100B, neuron-specific enolase and glial fibrillary acidic protein are the main NB of interest in cardiac surgery [73, 80–84]. Results on their availability as early brain damage markers are encouraging, although several issues need to be overcome before their inclusion in daily practice [82].

Among several NB currently investigated in CNS monitoring, S100B protein seems to be one of the most promising NB of brain damage detection and prognosis both in adult, pediatric and newborn patients [18, 85, 86]. While in non-CHD patients the usefulness of S100B in brain monitoring has been proven, the history of the protein in CHD adults, children and infants showed a Gaussian-like trend: outstanding at first, followed by a dramatic decay and finally rehabilitated.

S100B

S100B is an acidic, calcium-binding protein of low molecular weight (10.7 kDa), first identified by Moore as a protein fraction detectable in the CNS, particularly in glial and Schwann cells and in specific neuronal subpopulations [84–88]. The protein has a half-life of 30–60 min, and it is mostly eliminated by the kidney route (98%) [89]. S100B is involved in intracellular signal transduction via protein phosphorylation inhibition, enzyme activity modulation, calcium homeostasis dysregulation, and affects cell morphology via interaction with cytoplasmic cytoskeleton elements [85–91]. At physiological concentrations (around nM), the protein acts as a neurotrophic factor during neuronal development and regenerative processes [92–95]. Conversely, at high concentrations (sub-microM or microM), S100B manifests neurotoxic properties causing the cascade of pathophysiological events leading to cell apoptosis [85, 86, 95]. Recently, it has been suggested that S100B release occurs in isolated Schwann cells through a process that requires activation of the cell surface receptor, RAGE (receptor for advanced glycation end products). In particular, there is evidence that: i) S100B binds to the RAGE V-domain, ii) the high extracellular Ca^{2+} conditions might favor the formation of S100B multimers, and iii) S100B multimers cause RAGE dimerization or stabilization of preformed RAGE oligomers. Interestingly, at doses ≥500 nM S100B up-regulates RAGE expression in neuronal cell lines due to

RAGE-mediated reactive oxygen species (ROS) generation and the subsequent activation of MEK/ERK1/2 [93]. Therefore, these findings suggest that even at concentrations commonly thought to be protective towards neurons, S100B might turn neurotoxic in the presence of excess ROS generation.

Further sources of S100B

S100s are dimeric proteins constituting a major component of the cytosol of various cell types. A1B and BB dimers are mainly concentrated in the CNS. In detail, BB is mainly located in glial and Schwann cells but is also present in specific neuron sub-populations and in neural precursor cells [85, 86]. A1B dimer is also concentrated in extra-nervous tissues such as white fat, skeletal muscle, heart, liver, spleen and kidney [85, 86, 96]. In this light, the possibility that extra-source sites of concentration of the protein could somewhat affect its reliability as a brain damage marker has been hypothesized. To this end, Haimoto et al. investigated the differential distribution of S100 A and B dimers in non-nervous human tissues. They showed that, of the total amount of S100B found in different tissues during the post-natal period, the highest concentration was in the brain (538,000 μg, 90.9%), followed by the muscles (42,000 μg, 7.1%), the adipocytes (10,500 μg, 1.77%), the heart (1,000 μg, 0.2%), and the liver (200 μg, 0.03%) [96]. Another S100B extra-source is the placenta: the protein has been shown, by immunohistochemistry, to be localized in villous and intermediate trophoblast cells of the normal placenta at various trimesters of gestation. Concentration of S100B in the placenta has been found to be gestational-age-dependent [97–100].

Finally, S100B levels have been shown to reflect blood-brain barrier (BBB) integrity: changes in oxygen and carbon dioxide blood levels as well as metabolic CNS diseases can damage or change BBB permeability leading to a transport of the protein from brain to systemic circulation [101].

S100B measurement techniques

In the last few decades, many assays have been developed to improve detection of S100 protein in biological fluids: microcomplement fixation, radioimmuno, particle-counting, two-site immunoradioactive/IRMA (Sangtec 100, AD Sangtec Medical, Bromma, Sweden), immunoluminometric assay (Lia-mat Sangtec 100, AB Sangtec Medical, Bromma, Sweden) and ELISA (SynX Pharma, Toronto, Ontario, Canada). Immunoluminometric assays are mainly used because of their qualities: they are rapid, reproducible, reliable and low-cost tests. Technological progress has improved the sensitivity of assays, whose threshold has decreased from 1.5 to 0.2 μg/L and lower than 0.02 μg/L by using chemiluminescence (Liaison S100, Dietzenbach, Germany) [102].

Currently Roche Diagnostics and DiaSorin, two companies specializing in *in vitro* diagnosis, have offered automated analyzers able to determine S100B protein concentration in serum. Roche Diagnostics' (Meylan, France) electrochemiluminescence immunoassay has shown a lower limit of protein detection of about 0.005 μg/L, while by using DiaSorin assay the mean values are 27% higher than the former. Notably, both immunoassays can detect S100 dimers that contain S100B (S100BB and S100A1B) and provide a result within 18 min [103].

Recently bioMerieux Vidas (Marcy l'Etoile, France) has developed an automated enzyme-linked fluorescence assay with a lower threshold of 0.012 μg/L, analysis time of approximately 20 min and the ability to detect both S100B dimers [102–105].

S100B in adult OHS

In Table 2 the main results of S100B *pros* and *cons* as a NB both in adults undergone to OHS and CPB are reported.

Pros

Preliminary studies showed a S100B perioperative pattern characterized by an increase in blood protein levels from the onset of CPB, peaking at the end of the by-pass, and followed by a decline in the post-OHS period. In particular, a relationship has recently been observed between high S100B levels and post-OHS outcome, namely: i) short/long-term neurocognitive disorders with a sensitivity and specificity of 90% [106], ii) stroke, also correlating with the extension of CNS damage [107], iii) a series of neurological phenomena including delirium, sleep disorders, memory loss and cognitive impairment up to 8 weeks post-OHS [107–111]. Finally, the length of hospital stay has also been correlated with high S100B post-OHS levels [112]. Based on the aforementioned findings, it has been suggested that S100B assessment in the first post-operative day might not only be a useful marker of post-OHS neurological complications but also a tool for evaluating the efficacy/side-effects of new OHS approaches and neuroprotective strategies [107–113]. This especially holds for other peri-OHS and patient parameters. The former, included a positive correlation between

Table 2: Literature data on S100B patterns in adult patients undergone to open heart surgery and cardiopulmonary by-pass.

Ref.	Study	n	Assay	P/C	Main results
[107]	PS	20	IRMA	P	Higher S100B at 48 h after surgery correlated with the size of infarcted brain tissue and predicted median term survival.
[108]	PS	74	LIA	P	Higher postoperative S100B predicted early adverse neuropsychological and neuropsychiatric outcome.
[109]	PS	45	LIA	P	Patients with elevated S100B values have more sleep disturbances after cardiac surgery.
[110]	PS	130	IRMA	P	Higher S100B correlated with age, CPB duration bypass time and with impaired memory performance.
[111]	PS	100	LIA	C	No correlation between S100B and long-term cognitive impairment.
[115]	PS	32	LIA	C	Lower perioperative S100B levels in adults undergone to OHS without CPB than those with CPB.
[116]	PS	132	IRMA	C	Higher postoperative S100B from the surgical field and in the shed mediastinal blood. Autotransfusion interferes S100B availability as brain damage marker.
[117]	PS	20	LIA	C	Six-fold reduced S100B peak levels in the cell saving device group compared to the cardiotomy suction group.
[118]	PS	30	LIA, ELISA	C	S100A1B and S100BB analysis did not distinguish S100B cerebral from extracerebral sources in mediastinal blood.
[119]	M	411		C	Off-pump and on-pump CABG surgeries increase S100B in adult CHD patients within 24 h after on-pump CABG surgery.
[120]	PS	10	LIA	C	Increased serum S100B levels due to protein's mediastinal extra-source.
[121]	PS	21	LIA	C	Early increase in S100B correlated with markers of tissue injury outside the brain.
[122]	PS	40	LIA	C	Both intravenous UFH and subcutaneous LMWH administration induces increases in serum S100 concentration.
[123]	M	549		C	Lower S100B in the inhalation anesthesia group than in the TIVA group after CPB and 24 h after surgery.
[124]	PS	50	ELISA	C	S100B levels correlated with severe insulin resistance and stress hyperglycemia.

Ref., references; n, number; P, pros; C, cons; PS, prospective study; IRMA, immunoradiometric assay; LIA, luminescence immunoassay; CPB, cardiopulmonary bypass; OHS, open heart surgery; ELISA, enzyme-linked immunosorbent assays; M, metanalysis; CABG, coronary artery bypass graft surgery; CHD, congenital heart disease; UFH, unfractionated heparin; LMWH, low molecular weight heparin; TIVA, total intravenous anesthesia.

S100B and the duration of aortic cross-clamping, of DHCA, and of occurrence of cerebral emboli [107, 112, 114, 115]. The latter with pre-existing patient specific factors such as age, cerebrovascular complications, and renal impairment. This finding is noteworthy bearing in mind that the protein's concentrations are age-dependent [113].

Cons

Initial confidence in the correlation between S100B and brain damage has faded over the years following the demonstration that some early increases in serum protein levels may reveal the presence of an extra-cerebral S100B origin [115–118]. One of the main reasons may reside in the measurement of the protein during the use of new specific surgical devices such as a filter in the arterial line or heparin-coated surfaces and new OHS phases including the on-off-pump phase [114, 116]. Furthermore, the introduction of autotransfusion and mediastinal shed blood has been found to influence the S100B release from CPB phase up to 10 h post-OHS [116]. Moreover, cardiotomy suction has been suggested as a bias factor in increased S100B release during CPB [117].

The effects of surgical procedure deserve further consideration. These mainly regarded the absence of any perioperative S100B differences between: i) patients who had undergone OHS using a cell-saving device with CPB and in those operated on off-pump [119] ii) samples collected from pleural drainage of patients having a thoracotomy without CPB and those collected from mediastinal drains with CPB [120].

The effects of the different sites of sampling have been found to affect S100B reliability as a brain damage marker. In particular, higher protein levels (up to 1,000 times)

detected in blood from surgical wounds, bone marrow aspirate, and from traumatized mediastinal fat and skeletal muscle did not make it possible to distinguish cerebral from extracerebral origin of S100B. Authors concluded that an early increase in S100B resulted from extra-cerebral contamination, while a late increase (after 24–48 h) of S100B correlated with brain damage [118, 121]. However, the aforementioned confounding factors have been partly overcome by using a cardiotomy reservoir, thus reducing the total amount of extra-source protein.

Lastly, perioperative therapeutic strategies side-effects on S100B releasing in the systemic circulation has to be considered. This holds for unfractionated heparin and low molecular weight heparin administration routinely used for venous thromboembolism prophylaxis in OHS patients in which an increase of the total amount of S100 proteins members including at least one S100B monomer has been found [122]. This result could be due to heparin anti-inflammatory action via inhibition of S100 binding to RAGE [122].

Finally, anesthesia methods and glucose metabolic impairment have been found to interfere with S100B release [123, 124]. In detail, lower S100B levels have been found in patients subjected to generally inhaled rather than intravenous anesthesia, suggesting a brain protecting role [123]. Conversely, hyperglycemia led to higher S100B levels, indicating insulin-resistance and stress hyperglycemia as enhancers of OHS brain injury in these patients [124].

S100B in infants and children OHS

In Table 3 the main results of S100B *pros* and *cons* as a NB both in adults undergone to OHS and CPB are reported.

Pros

Following the observations on adults, S100B has been assessed in CHD infants subjected to OHS to monitor brain stress in different perioperative phases. In particular, studies evaluating CNS stress during OHS showed significantly higher protein levels: i) either before or after the end of surgical procedure [41]; ii) during and after OHS in infants complicated by early perioperative death and/or brain damage [41, 125–128] when compared to infants without perioperative complications; iii) as an index of increased cerebrovascular resistance and of changes in cerebral oxygen saturation by means of NIRS perioperative

Table 3: Literature data on S100B patterns in congenital heart diseases infants undergone to open heart surgery and cardiopulmonary by-pass.

Ref.	Study	n	Assay	P/C	Main results
[125]	RS	75	LIA	P	Perioperative S100B *z*-scores were significantly higher in the cases developing neurological deficits.
[128]	PS	32	IRMA	P	A significant correlation between S100B and increased cerebrovascular resistance.
[129]	PS	18	ELISA	P	Higher S100B in the perioperative period (particularly CPB) in cases with a wide cerebral arteriovenous difference measured by NIRS.
[130]	PS	109	LIA	P	Perioperative S100B inversely correlated with the size of the ascending aorta in hypoplastic left heart syndrome and suggested as a marker for pre-existing brain injury and mortality.
[131]	CCS	48	LIA	P	Higher S100B concentrations in CHD cyanotic infants.
[132]	PS	43	LIA	P	Higher S100B in CHD cyanotic infants undergone to uncontrolled hyperoxic reoxygenation in the rewarming-CPB phase.
[134]	RCT	79	ELISA	P	Controlled reoxygenation rewarming-CPB phase significantly decreased S100B levels in CHD infants (single-ventricle).
[137]	RCT	67	ELISA	P	S100B significantly differed between the normoxic and hyperoxic groups at different CPB phases.
[139]	PS	90	LIA	C	Higher S100B in pleural, pericardial and peritoneal fluids before and after cardiac surgery in CHD infants.
[144]	PS	26	LIA	P	In CHD infants S100B protein is not affected by an adipose tissue extra-source release.
[145]	RCT	60	LIA	P	Higher S100B in the phentolamine-treated group than in controls from the rewarming-CPB phase up to 12 h from surgery.

Ref., references; n, number; P, pros; C, cons; RS, retrospective study; LIA, luminescence immunoassay; PS, prospective study; IRMA, immunoradiometric assay; ELISA, enzyme-linked immunosorbent assay; CPB, cardiopulmonary by-pass; NIRS, near infrared spectroscopy; CCS, case-control study; CHD, congenital heart disease; RCT, randomized control study; h, hours.

Table 4: Food and Drugs Administration and European Medicine Agency criteria for perinatal neuro-biomarkers inclusion in clinical guidelines. Comparison between adult and pediatric obtained results.

S100B	Adults	Ref.	Infants	Ref.
Indicator of CNS damage	Y	[81, 101, 106, 114]	Y	[74, 105, 125, 126]
Degree of injury	Y	[81, 114]	Y	[105, 125, 126, 131, 132]
Lesion extension	Y	[106, 107]	Y	[74, 125, 126]
Longitudinal monitoring	Y	[106–113]	Y	[75–79, 84, 85, 98, 99, 127–129]
Pediatric/adult population	Y	[106]	Y	[106]
Available kits	Y	[102–105]	Y	[102–105]
Reference range	Y	[147]	Y	[36]
Biological fluid	CSF, PB	[147]	CSF, PB, AF, CB, U, S, M	[36, 75–79, 84, 85, 98, 99]

CNS, central nervous system; Y, yes; CSF, cerebrospinal fluid; PB, peripheral blood; AF, amniotic fluid; CB, cord blood; U, urine; S, saliva; M, milk.

monitoring, particularly the rewarming phase [129], iv) in cyanotic CHD infants when compared to non-cyanotic CHD because of their increased chance of brain stress/damage perioperative exposure [130, 131], and v) in infants who had undergone CPB weaning with or without the controlled rewarming re-oxygenation strategy [132–136]. The neuroprotective action of re-oxygenation has been confirmed by a lower S100B release in systemic circulation both in animal models and in cyanotic CHD infants [133–138]. Altogether, it is reasonable to argue for the usefulness of S100B as a predictor of brain distress/damage as well as of a potentially fatal outcome.

Cons

Despite the aforementioned promising results, the fate of S100B as a diagnostic tool of CNS damage in the perioperative period of CHD infants is still controversial and debated. As for adults the protein was progressively abandoned for CNS monitoring in CHD children due to a putative extra-source of protein bias [118, 139–143]. This especially refers to its potential release from cardiac adipose tissue during CPB phases [140, 143]. Another non-neural S100B source might be the pericardial fluid in which the protein has been measured in CHD children during OHS [139]. Finally, further studies aimed at investigating the adoption of new cardiotomy reservoirs and of controlled re-oxygenation effects on S100B release are needed in pediatric patients.

Conclusions

Today, as for non-CHD high risk infants a trustable NB able to predict perioperative brain damage in CHD children is still eagerly awaited. At this stage, there are no clinical protocols or guidelines approved by FDA, NIH or by the EMA validating S100B assessment in CHD children as for traumatic brain injury. The issue is noteworthy taking into consideration the lack of studies in children and particularly in adults fulfilling the items requested by FDA, EMA and NIH (Table 4).

Before answering the question: *"Does S100B behave as a friend or an enemy in the management of OHS?"* the following confounding points affecting the protein's reliability as a predictor of CNS damage need to be addressed:

(1) A clear dichotomy has to be taken into account between adult and pediatric patients. The main differences regard: i) the diseases subjected to surgical treatment (acquired vs. congenital) [1–4, 5], ii) CPB strategy (pH vs. α-stat) [50], iii) degree of CPB length, the need of hypothermia and of DHCA that are not often necessary for adults, iv) clinical history characterized by most common pre-OHS medical conditions affecting cardiovascular, metabolic, renal and CNS systems instead of pre-existing multiorgan congenital/genetic disorders [1–4, 46], and iv) adults vs. children multiorgan adaptation to CPB widely accepted as a deliberate hypoxic-ischemic reperfusion damage representing the price to pay during OHS repair. This especially refers to different pediatric cardiovascular and cerebrovascular anatomical and physiological characteristics in terms of immaturity, smaller circulating blood volume and higher oxygen consumption rate [50].
(2) The design of the trials themselves in terms of small cohort sizes, lack of multicenter investigations, heterogeneity of neurological complications and of CHD investigated (cyanotic, non-cyanotic).
(3) The operator-dependent heterogeneity of OHS techniques varying from center to center, which can surely affect S100B reliability.
(4) The advances in the devices and strategies recently used for CPB performance (cardiotomy reservoir, controlled

re-oxygenation, on-off pump) that can constitute a bias in the evaluation of S100B reliability as a perioperative CNS damage diagnostic test.

(5) Previous data on the presence of non-neural S100B sources, in adults and children who have undergone OHS, thus affecting the reliability of the protein as a brain damage marker warrants further consideration. The main issue regards the release of S100B from adipose tissue under different perioperative conditions and sites of concentration such as: sternotomy, on-off-pump phase, autotransfusion and shed mediastinal blood, cardiotomy suction, thoracic and pericardial drainage [117, 121]. However, no data, at this time, have been provided regarding the measurement of the amount of adipose tissue released during OHS either in adults or pediatric patients. The issue is of relevance bearing in mind that, in the absence of any related endocrine disorder, the total amount of adipose tissue is age-related and significantly higher in children than in adults. Notably, the absence of any difference in blood levels of a well-established biomarker of circulating adipose tissue such as adiponectin, in CHD, OHS-CPB treated children, offers additional information on the present controversial and debated issue [144]. It is noteworthy, in this respect, that other intra-operatory events can be related to an exaggerated S100B release in systemic circulation such as: i) hypoxia-hyperoxia insults occurring during CPB cooling and rewarming phases [128, 129], ii) changes in brain blood barrier permeability temperature and CPB-management-dependent techniques (anesthesia, on-off pump, DHCA) [82, 83, 139], and iii) cyanotic or non-cyanotic CHD [128]. Altogether, taking into consideration that adipose tissue accounts for 1.77% of the total amount of S100B, the possibility that during OHS and CPB it could somewhat affect S100B level in systemic circulation, and its reliability as brain damage marker is remote.

(6) Different protein assessment techniques and assays performed in the studies herein reported, each of which measured S100 BB or A1B dimers, deserve further discussion. The issue is noteworthy since A1B dimer is not brain tissue-specific but is also concentrated in extra-nervous tissues (i.e.: white fat, skeletal muscle, heart, liver, spleen and kidney) [88, 89, 103–106, 146]. In conclusion, the present overview supports the notion that S100B protein assessment in biological fluids of patients who have undergone OHS and CPB could be a useful diagnostic tool of perioperative CNS stress and damage. Further studies measuring contemporary adiponectin and S100B protein in carefully selected study populations are needed to shed further light on this currently much-debated and controversial issue.

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