Biochemical markers of neurologic injury in cardiac surgery: The rise and fall of S100 β

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With the change in patient population toward older and sicker patients undergoing cardiac surgery, neurologic injury has emerged as perhaps the most important perioperative complication, and its frequency increases exponentially with increasing age.¹ Particular attention has been paid to the role of cardiopulmonary bypass per se² and thromboembolization from the ascending aorta.³ However, neurologic injury is not limited to only stroke and coma¹; increasingly there is a focus on the more subtle neurocognitive dysfunction and its consequences on quality of life.^{4,5}

The majority of cases of gross neurologic injury do not represent a diagnostic problem, as at the time of diagnosis the injury is usually manifest and irreversible. Neurocognitive dysfunction, however, is less accessible for quantification, which requires time-consuming neuropsychologic testing. With only a few exceptions, such testing has been unavailable for the cardiac surgeon. Prompted by the increasing awareness of neurologic injury, as well as the emergence of minimally invasive cardiac surgery, there is at present an increasing interest in cognitive testing. However, such testing will remain a research method and not available in everyday clinical practice because of the time and manpower it consumes.

A biochemical marker in the blood of the patients—"a troponin of the brain"—would represent a revolution in the investigation and diagnosis of neurologic injury in cardiac surgery. A serum marker could potentially identify which aspect(s) of cardiac surgery are responsible for cognitive dysfunction and evaluate the efficacy of alternative surgical techniques. Additionally, if marker concentrations during or directly after surgery could be related to cognitive dysfunction or shown to predict gross neurologic injury that became clinically evident after some hours (or days), then potentially neuroprotective interventions might be indicated.

The ideal biochemical marker should have the following properties:

1. Central nervous specificity
2. Rapid and significant release into blood after injury, preferably within minutes
3. Elimination within a few hours
4. Rapidly and readily obtainable assay results
5. Predictability of serious injury from an early sample, eg, at the end of surgery
6. Relationship of marker concentration to the degree of injury, quantifying the full range from subtle cognitive deficits to gross injury
7. Inexpensive

During the past two decades a variety of substances have been suggested as possible biochemical markers of brain injury, such as adenylate kinase, creatinine phosphokinase isoenzyme BB, lactate, myelin basic protein, S100 β , and neuron-specific enolase.⁶ Recently, glial fibrillary acidic protein has been added to this list,⁷ but its potential role is unknown. Most of these substances have methodologic problems: for instance, adenylate kinase and lactate have to be sampled directly from cerebrospinal fluid, and creatinine phosphokinase isoenzyme BB lacks brain specificity. The value of neuron-specific enolase was also recently shown to be doubtful

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Received for publication July 3, 2001; accepted for publication July 13, 2001.

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J Thorac Cardiovasc Surg 2001;122:853-5

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0022-5223/2001 \$35.00 + 0 12/1/119055

doi:10.1067/mtc.2001.119055

because of its association with hemolysis caused by destruction of erythrocytes.⁸

S100 β appeared to fulfill many of the above criteria of an ideal marker.^{6,9,10} Serum S100 β increases not only after cardiac surgery, but also in Alzheimer disease, Down syndrome, minor and major head injury, acute stroke, and after cardiac arrest.⁹ It has been suggested to be a prognostic predictor for the long-term consequences of minor head injuries and the degree of anoxic brain injury after cardiac arrest.⁹

Cardiac surgery causes an increase of serum S100 β after less than an hour (ie, before cannulation), a further increase to maximum blood levels at the end of cardiopulmonary bypass, and thereafter it rapidly declines,^{6,9} although occasionally with a late rise. Serum S100 β has been correlated with age, duration of cardiopulmonary bypass, duration of aortic cross-clamping, duration of deep hypothermic circulatory arrest, number of cerebral emboli during surgery, preoperative cerebrovascular complications, and preoperative renal impairment.⁹ The use of a filter in the arterial line or heparin-coated surfaces reduces postoperative S100 β levels.⁹ There are anecdotal reports that patients with operative cerebral injuries have higher concentrations of S100 β at the end of surgery.^{11,12} The relation of S100 β to neurocognitive dysfunction is controversial, but most studies do not find such a correlation.

These findings initiated the tremendous interest in S100 β , which was rapidly adopted as *the marker* of cerebral injury until recent findings suggested the presence of a significant noncerebral contribution. Patients operated on off-pump were shown to lack the large increased concentration seen after bypass, but an assay with increased sensitivity revealed a puzzling increase after only the prebypass surgical trauma.¹³ Jönsson and associates¹⁴ sampled blood every hour for the first 10 hours postoperatively, detected brief elevations of S100 β that coincided with the time points of auto-transfusion, and found a 20-fold increase of S100 β in the mediastinal shed blood compared with the regular blood samples. Anderson and colleagues^{15,16} showed that if the cardiomy suction was replaced by a cell-saving device during surgery with cardiopulmonary bypass, the serum S100 β concentrations during the whole perioperative period were indistinguishable from those of patients operated on off-pump. S100 β in the cell-saving reservoir blood was 10-fold greater than the maximum serum S100 β in patients undergoing conventional coronary artery bypass surgery with cardiopulmonary bypass using a cardiomy suction. Pleural drainage blood from patients having a thoracotomy (no cardiopulmonary bypass) contained equally large S100 β concentrations as blood from mediastinal drains after on-pump cardiac surgery.¹⁶ Very high levels of S100 β were detected in blood from the surgical wounds, from bone marrow aspirate, in mediastinal fat, and in skeletal muscle—concentrations that were up to 1000 times higher than the preoperative blood concentrations.¹⁶ Brain specificity was not improved

by separate analysis of the two dimer subgroups that comprise S100 β as it is commercially assayed.¹⁶ Both dimers appear in serum after surgery and both arise from extracerebral sources, especially traumatized fat and muscle tissue.

Hopes to use serum S100 β to screen patients who have had head trauma are clouded by the finding that even trauma patients *without* head injury have increased concentrations of serum S100 β , particularly after bone fractures, but even after limited soft tissue trauma and burns. These noncerebral contributions limit the usefulness of serum S100 β in neurosurgery.¹⁷ Serum S100 β increases seen after accidental or only surgical trauma (such as after off-pump surgery or on-pump surgery without a cardiomy reservoir) may be completely explained, although a cerebral contribution cannot be excluded, by capillary and lymphatic uptake into the circulation of the small (11-kd) S100 monomer due to the high concentration difference between mediastinal blood and the bloodstream.¹⁶

Consequently, extracerebral sources of S100 β make the interpretation of the early S100 β blood concentrations difficult, and no valid conclusions concerning neurologic injury in cardiac surgery can be drawn from the early release. To a large extent, the correlations previously detected for S100 β levels after cardiopulmonary bypass can be related to the use of the cardiomy suction: a longer operation or more complicated patient population means that more blood is suctioned from the mediastinum with increased return of mediastinal blood to the circulation, and thus the higher serum S100 β concentration. All previous data on S100 β should be reevaluated in light of this knowledge. The similarity of release between on-pump (when a cell saving system is used) and off-pump surgery suggests that *cardiopulmonary bypass per se does not release S100 β* .^{15,16} These data imply that the early sampling of S100 β is useless in detecting neurologic damage after conventional cardiac surgery using cardiopulmonary bypass because of the high background noise of S100 β release from extracerebral sources. Late increases in serum S100 β , after 24 to 48 hours, have been related to perioperative cerebral complications like stroke, delayed awakening, and confusion.^{9,12} Unfortunately, this is neither helpful nor really interesting, because at this stage the brain injury is already manifest and irreversible and may be quantified in other, probably more precise ways. The potentially most interesting use of the serum S100 β concentration would have been a detectable contribution from the brain at or immediately after the operation.

Two possibilities for the use of early S100 β release exist:

1. Can an early high level of serum S100 β predict that a neurologic injury has occurred? This is probably only possible if the cardiomy reservoir has not been used. The contributions from surgical trauma are smaller, but as cardiopulmonary bypass makes no distinguishable

addition, any correlation with cognitive dysfunction is below the level of detection.

2. Sampling of cerebrospinal fluid for measurements of S100 β may avoid the above problems, although a spinal tap may create additional problems. Spinal fluid drainage presents a unique opportunity to compare cerebrospinal fluid and blood levels of S100 β .

In this issue of the *Journal*, Kuniyara, Shiiya, and Yasuda¹⁸ compared values in serum and in cerebrospinal fluid of patients undergoing surgery for thoracoabdominal aneurysms. The number of patients in each group is small, but the study shows higher sensitivity and earlier release of S100 β into the cerebrospinal fluid when spinal injury occurred. More such studies are needed to investigate whether S100 β has any place at all as an early marker of neurologic injury in cardiovascular surgery. At the present time, using serum S100 β concentrations immediately after the end of bypass as a marker of neurologic injury is *not acceptable if a cardiomyotomy suction has been used*. In addition, any tissue damage will limit its usefulness, particularly in diagnosing the subtle changes of greatest interest.

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