CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

COMMENTARY: BIOCHEMICAL MARKERS OF BRAIN INJURY AFTER CARDIAC SURGERY

John W. Hammon, Jr, MD
David Stump, PhD

The use of biochemical markers as monitoring tools for disease or organ damage is widespread and universal. Much work was carried out in the 1960s and 1970s in the characterization of creatine kinase and its isoenzymes to determine whether myocardial damage occurred after cardiac surgery. Only through careful determination of the presence of isoenzymes and the sites and rates of expression and degradation was useful information gathered. An ideal biochemical marker should be organ specific, quantitative, and predictable, and its kinetics should be understood. Four articles in this issue address the use of biochemical markers to estimate potential brain injury in patients undergoing a variety of cardiac operations. The results presented in these manuscripts reflect the fact that the development of a biochemical marker for cerebral injury is limited by several unique problems. Because the brain is not homogeneous, the site of an injury as opposed to the size of an injury determines the degree of functional impairment. Within the brain, there are a variety of cell types, all differing in cellular architecture and makeup. The blood-brain barrier further complicates the picture.

In the papers contained in this issue, S-100 proteins and neuron-specific enolase (NSE) have been used to estimate brain injury after cardiac surgery. Much has been written regarding these two markers of cerebral damage. The purpose of this editorial is to try to clarify the results presented in this issue as they relate to our current knowledge.

S-100 proteins are a group of acidic, calcium-binding proteins found in high concentrations in the nervous system.¹ They are dimers of the $\alpha\beta$ subunits presenting in various concentrations in glial and Schwann cells, as

well as striated muscle, heart, and kidney. These proteins are metabolized and excreted by the kidney with a half-life of 113 minutes in plasma.² The normal, in vivo level, of S-100 β is undetectable by currently available assays. NSE is a dimeric, glycolytic enzyme located in neurons.³ It may also be produced by small cell lung cancer and tumors of neuroendocrine origin.⁴ Unfortunately, it is also present in platelets and erythrocytes, which can lead to errors in interpretation because a small degree of hemolysis or platelet damage can substantially increase plasma levels.⁵

After brain injury, S-100 β and NSE are detectable in the cerebral spinal fluid. After an acute stroke, serum levels of both S-100 and NSE are elevated.⁶ Unlike NSE, S-100 β levels appear to be related to the volume of brain damage and clinical outcome in acute stroke.⁷ Because of the relationship to the volume of injured brain, many investigators have attempted to use postoperative S-100 β levels to estimate the amount of brain injury in patients undergoing cardiac surgery. In our own experience, as well as the experience of others including papers published in this issue, the amount of S-100 begins to rise in the serum during cardiopulmonary bypass and reaches a peak 24 to 36 hours after the operation. This is similar to the findings in acute stroke. Because the isoforms of S-100 are found in high concentrations in Schwann cells and glial cells, which are prevalent in the white matter of the brain, we postulate that the release of S-100 β during cardiopulmonary bypass reflects changes in white matter.⁸ Harris and associates⁹ have reported that patients studied preoperatively and postoperatively with cerebral magnetic resonance imaging demonstrate cerebral edema predominately in white matter. The mechanism of the brain swelling is uncertain but is probably related to a combined effect of hemodilution and membrane changes in the brain, perhaps related to the generalized inflammatory reaction produced by cardiopulmonary bypass. This swelling is unaffected by cardiopulmonary bypass temperature and disappears within 7 days after the operation.¹⁰

Because isoforms of S-100 are located in multiple sites in the body, there has been much speculation as to elevated S-100 β levels in patients exposed to cardiopulmonary bypass who do not have clinical brain injury.

From the Departments of Cardiothoracic Surgery,^a Anesthesiology, and Neurology,^b Wake Forest University School of Medicine, Winston-Salem, NC.

Received for publication Nov 5, 1999; accepted for publication Nov 11, 1999.

Address for reprints: John W. Hammon, Jr, MD, Professor of Surgery, Department of Cardiothoracic Surgery, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1096.

J Thorac Cardiovasc Surg 2000;119:130-1

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0022-5223/2000 \$12.00 + 0 12/1/104174

Johnsson¹¹ has recently postulated that the increased levels of S-100 during and after cardiopulmonary bypass may be related in part to a previously overlooked extracerebral source, which is thought to be lipolysis of fat from mediastinal tissue that enters the circulation via cardiotomy suction, or retransfusion of shed blood postoperatively.

Very few patients undergoing cardiopulmonary bypass have acute stroke. Therefore other measures of brain function have been used to quantitate cerebral injury in patients after cardiopulmonary bypass. Neurocognitive or neuropsychologic testing has been used to quantitate brain function preoperatively and postoperatively and has been found to be abnormal for at least 7 to 30 days in as many as 60% of patients undergoing cardiopulmonary bypass for a variety of operations.¹² Unfortunately, it has been difficult to establish a consistent correlation between the results of S-100 elevations and abnormal neuropsychologic performance after surgery.¹³ The reasons for this are intuitive. Abnormal neuropsychologic performance is primarily related to defects in gray matter, whereas white matter alterations seem to be responsible for elevations of S-100. Therefore it may be difficult to correlate these two measures of brain injury postoperatively although the two may be complementary.

In this issue, Svensson and associates were able to find a correlation between early changes in neuropsychologic performance and S-100 elaboration. It is important to note that their model (patients undergoing circulatory arrest for aortic arch procedures) was the most severe model and exposed the brain to potentially injurious generalized hypoperfusion. Therefore the changes seen in Svensson's patients would be generalized and not related to gray or white matter exclusively. Even with the elevations of S-100 β and decrements of cognitive function seen 1 week after the operation, no patients had acute stroke and had returned to normal cognitive function in 1 month. It is reasonable to assume that membrane changes in glial cells are responsible for both white matter edema and elaboration of S-100 β . The time courses for the disappearance of both cerebral edema and serum levels of S-100 β are similar.

The critical question that would benefit surgeons performing cardiac operations is this: Do small elevations of S-100 during and after cardiopulmonary bypass indicate permanent brain injury? This question cannot be accurately answered at this point, but some generalizations can be made. Because postoperative S-100 levels are not consistently correlated with transient neurologic or neuropsychologic abnormalities, it is unlikely that mild to moderate elevations of S-100 are associated with clinically detectable permanent brain injury. Moreover, our clinical data suggest that S-100 levels are more related to the duration of cardiopulmonary

bypass and not to the number of emboli delivered to the brain, as measured by Doppler ultrasound, nor to the postoperative neuropsychologic performance.¹⁴ In addition, since S-100 is cleared by the kidneys, studies measuring S-100 should correlate the serum levels with the clearance. This will be very similar to the relationship between serum creatinine levels and the creatinine clearance in patients after cardiac surgery.

It appears certain that articles in which biochemical markers have been used to measure brain injury will continue to appear. As investigators more clearly identify the significance of elevated markers of brain injury, the clinical role for these findings will be further elucidated. At this point, this role is not yet clear.

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