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ORIGINAL ARTICLE

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Elevated serum levels of S-100 after deep hypothermic arrest correlate with duration of circulatory arrest

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Abstract *Objective.* Cerebral damage is a major problem after reconstructive surgery of the aortic arch and the descending aorta. Current protective strategies, including deep hypothermia and retrograde cerebral perfusion, are used to prolong the tolerated duration of circulatory arrest, and the latter may also decrease the possibility of air/particle embolization. The aim of the current study was to investigate whether the neurochemical marker S-100 is related to the duration of circulatory arrest, when the influence of embolic injury has been minimized by the use of retrograde cerebral perfusion during the last part of circulatory arrest.
Methods. Arterial serum levels of S-100 were followed before, during and after reconstructive surgery of the thoracic aorta during deep hypothermic arrest in ten adults. Retrograde cerebral blood perfusion was used during the latter part of the arrest period in eight of the ten patients. Neurologic status was followed daily.
Results. All patients survived the operation. The median (range) duration of cardiopulmonary bypass (CPB) was 184.5 (121–386) min. The median duration of circulatory arrest and retrograde cerebral perfusion was 50 (3–118) min and 16 (0–84) min, respectively. S-100 increased from 0.10 (0.02–0.18) μg/l preoperatively to 2.37 (0.64–10.80) μg/l after CPB ($P<0.01$), followed by a decrease to 0.79 (0.21–2.64) μg/l on the first postoperative day ($P<0.01$). The duration of circulatory arrest correlated with S-100 levels after CPB ($r_S=0.71$, $P<0.05$) and even better with the S-100 levels on the first postoperative day ($r_S=0.83$, $P<0.01$). However, there was no significant correlation between duration of arrest and duration of CPB. The duration of circulatory arrest without retrograde cerebral perfusion correlated well with S-100 levels on the first postoperative day ($r_S=0.88$, $P<0.01$), but not significantly with S-100 levels after CPB.
Conclusions. S-100 levels after aortic surgery with deep hypothermic arrest correlate with the duration of circulatory arrest, indicating that the duration of circulatory arrest is damaging to the brain despite the use of deep hypothermia and partial retrograde cerebral perfusion. The highest correlation between S-100 and duration of arrest was seen on the first postoperative day. S-100 appears to perform well under clinical circumstances as a sensitive and discriminative marker for neuronal injury. [Eur J Cardio-thorac Surg (1996) 10: 1107–1113]

Key words Brain damage · Cardiac surgery · Cerebral perfusion · Cardiopulmonary bypass

Introduction

Recent technical advances in reconstructive surgery involving the aortic arch include open aortic anastomosis and exclusion of the cerebrovascular tree from the circulation during circulatory arrest. However, the effectiveness of cerebral protection is very important for the outcome. Current strategies to protect the brain include deep hypothermia to depress cerebral metabolism enough to tolerate a period of circulatory arrest, but the safe limit of the arrest is still controversial. New strategies to extend the tolerated period of circulatory arrest include retrograde cerebral blood perfusion, which also has the advantage of diminishing the risk of embolic injury to the brain before normal antegrade cerebral perfusion is reinstated.

Cerebral dysfunction after cardiac surgery and after reconstructive surgery involving the aortic arch in particular is of major concern, with an often very long and costly reconvalescence [4]. The estimated cost of a stroke in terms of hospitalization, rehabilitation and lost earnings potential is in the range of $ 250,000 per patient. Major strokes are easily detected postoperatively, whereas minor or diffuse lesions caused by microembolization or cerebral hypoperfusion may require more sophisticated methods to be detected, including magnetic resonance imaging or cognitive function tests. This problem was recently addressed at the first international "Conference on CNS dysfunction after cardiac surgery: Defining the problem", where a statement of consensus on assessment of neuro-behavioral outcome was approved [22]. A valuable way of detecting cerebral damage is to follow an early marker for cerebral injury in serum. Earlier studies in this field involved the analysis of cerebrospinal fluid [1, 20] or serum markers, including creatine-kinase BB and neurone specific enolase [9, 19]. Experimental studies in gerbils indicate that a 30-min period of total circulatory arrest at 18–20 °C is nearly uniformly safe and results in little structural or functional brain damage [23]. There is a considerable probability of brain damage when the period of circulatory arrest exceeds 45 min at this temperature, with the probability increasing as the arrest time lengthens. Studies of CK-BB in children undergoing deep hypothermic surgical procedures with a period of circulatory arrest also suggest an exponential increase in CK-BB levels after long periods of circulatory arrest. Recent studies have confirmed the suspicion that subclinical cerebral injury occurs in a significant proportion of neonates after prolonged arrest [5, 16] and that some degree of transient neurologic injury occurs in a substantial proportion of adult patients undergoing prolonged hypothermic arrest during aortic arch surgery [10].

The intracellular calcium binding protein S-100 is a dimeric protein with alpha or beta subunits, where the beta subunit is highly brain specific. The beta-beta units are present in glial and Schwann cells, whereas the alpha-beta subunits appear in glial cells but not in Schwann cells [3, 14]. Increased levels of S-100 in both serum and cerebrospinal fluid have been reported after major [11, 17] and minor head injury [13]. The finding of increased serum levels despite normal computed tomography scans in the latter group suggests a protein leakage through the blood-brain barrier due to cell injury. S-100 is eliminated through the kidneys and studies on elimination indicate a half-life of 2 h [24].

The aim of the current study was to investigate if the neurochemical marker S-100 is related to the duration of circulatory arrest, when the influence of embolic injury has been minimized by the use of retrograde cerebral perfusion during the last part of circulatory arrest.

Patients and methods

Ten consecutive patients undergoing surgery of the thoracic aorta, involving the aortic arch, at Huddinge University Hospital and Karolinska Hospital, were included in the study. All surgical procedures were conducted with a period of circulatory arrest. Patient data are presented in Table 1. None of the patients had a history or signs of cerebrovascular disease preoperatively. The study protocol conformed to the rules of the Helsinki declaration and was approved by the Ethics committee of Karolinska Institute. Informed consent was obtained from patients participating in the study.

Clinical management

All patients were premedicated with morphine 0.125 mg/kg and scopolamine 5 μg/kg 1 h before they were taken to the operating room, where radial and femoral artery catheters, and one peripheral and three central venous lines were inserted. Additionally, a retrograde jugular catheter was introduced over a guide-wire, which in turn had been advanced until its tip corresponded to the position of the jugular bulb [25]. Electrocardiogram lead V_5, mean arterial pressure (MAP), central venous pressure (CVP), and rectal and nasopharyngeal temperatures were monitored continuously.

Table 1 Patient data

Patient	Gender	Age	Aortic disease
1	female	71	Arch aneurysm
2	male	72	Thoracic dissection
3	female	73	Thoracic aneurysm
4	male	74	Ascendens, arch aneurysm
5	male	70	Arch, descendens ruptured aneurysm
6	male	47	Arch aneurysm
7	male	77	Arch, descendens aneurysm
8	female	64	Ascendens, arch aneurysm
9	female	71	Ascendens, arch aneurysm
10	female	62	Ascendens, arch dissection
Median		71	
Range		47–77	

Anesthesia was induced with fentanyl 7–15 μg/kg and midazolam 0.05–0.1 mg/kg. Induction of anesthesia was supplemented by a single bolus of thiopental 0.5–2 mg/kg and barbiturates were not given afterwards. Tracheal intubation was performed after pancuronium 0.1 mg/kg. The patients were ventilated with oxygen and air, until shortly before cardiopulmonary bypass (CPB), when only oxygen was used. Droperidol (0.1 mg/kg) was given at the start of surgery and anesthesia was maintained with intermittent doses of fentanyl 1–2 μg/kg and midazolam. Additionally, isoflurane at an end-tidal concentration of 1% or less was administered when needed before and/or after CPB. Cardiopulmonary bypass was conducted using only membrane oxygenators. A systemic pump flow rate of 2.4–2.7 l/min×m^2 was maintained during normothermia and reduced during hypothermia. A nasopharyngeal temperature of less than 20 °C was achieved before the induction of circulatory arrest. During circulatory arrest, retrograde cerebral perfusion was accomplished by perfusing the superior vena cava with oxygenated blood in eight of the ten patients. The jugular bulb pressure was kept between 25 and 30 mmHg by varying the pump flow between 250 and 600 ml/min. Retrograde cerebral perfusion was not used in two patients, where the descending aorta was approached through a left-sided thoracotomy. Rewarming was continued until the rectal temperature had reached 30–35 °C. Ventilation of the lungs during CPB was commenced after declamping of the aorta. Alpha-stat pH-management was employed. Myocardial protection was accomplished with retrograde blood cardioplegia, in all but two patients. Neurologic status was followed daily during the hospital stay.

Arterial serum levels of S-100 were followed preoperatively before the start of surgery, directly after completing CPB and on the 1st postoperative morning.

S-100 assay analytical method

The serum concentration of S-100 protein was measured using an immunoradiometric assay kit, IRMA, (Sangtec 100, AB Sangtec Medical, Bromma, Sweden) using two capture monoclonal antibodies (SMSK 25 and SMSK 28) and one tracer antibody (SMST 12) directed against different epitopes on the beta-subunit of bovine S-100 protein. The capture antibodies are bound to plastic beads, and the tracer antibody is labelled with ^{125}I. Thus, the test for Sangtec 100 measures both the beta-beta and the alpha-beta, but not the alpha-alpha, isoform of the S-100 protein. The original kit was slightly modified by the inclusion of one calibration-point at 0.20 μg/l. The coefficient of variation on the duplicates were 2.0% and 6.9% at the levels 3.1 and 29.6 μg/l, respectively.

Eighty-one healthy adults were also included in the study to establish a reference interval for serum levels of the S-100 protein. All but five had serum concentrations of S-100 below 0.10 μg/l. These five healthy subjects had the following values: 0.10, 0.10, 0.11, 0.11, and 0.14 μg/l, respectively. Thus, more than 90% of the healthy subjects had S-100 levels below 0.10 μg/l.

Statistics

The results are expressed as *medians and ranges*. The Wilcoxon test for pair differences, Mann-Whitney U-test and rank Spearman regression test were used.

Results

The median duration of CPB was 184.5 with a range of 121–386 min. A nasopharyngeal temperature of 18 °C (range 15.0–19.2 °C) was achieved before the start of circulatory arrest. The median duration of circulatory arrest and retrograde cerebral perfusion during circulatory arrest was 50 (range 3–118) min and 16 (range 0–84) min, respectively. The median duration of circulatory arrest minus retrograde cerebral perfusion was 26 (range 3–70) min. S-100 increased from a median preoperative level of 0.10 μg/l (range 0.02–0.18) to 2.37 μg/l (range 0.64–10.8) post-CPB ($P<0.01$), followed by a fall to 0.79 μg/l (range 0.23–2.64) on the 1st postoperative day ($P<0.01$). All patients had their highest S-100 serum levels directly after CPB, followed by a decrease in serum levels in all patients on the 1st day after surgery. Figure 1 illustrates changes in individual serum levels of S-100 values before surgery, directly after CPB and on the 1st postoperative day. The duration of circulatory arrest correlated significantly with S-100 levels after CPB ($r_S=0.71$, $P<0.05$, Fig. 2) and with a higher correlation coefficient on the 1st postoperative day ($r_S=0.83$, $P<0.01$, Fig. 3). However, there was no significant correlation between the duration of CPB and S-100 levels after CPB ($r_S=0.66$, n. s.) or S-100 levels on the 1st postoperative day ($r_S=0.31$, n. s.).

The duration of circulatory arrest minus the duration of retrograde cerebral perfusion, i. e. the duration with absent cerebral perfusion, correlated well with S-100 levels on the 1st postoperative day ($r_S=0.88$, $P<0.01$, Fig. 4), but not significantly with S-100 levels after CPB ($r_S=0.62$, n. s.). All patients survived the operation. Seven patients were extubated within 36 h and three patients were extubated within 12 days. The patient with the highest S-100 values, both after CPB and 1 day after surgery, presented a postoperative stroke, which was verified as several frontal cerebral infarctions on computed tomography. This patient, no. 6, was initially stuporous, but recovered and was finally extubated 10 days after surgery. Patient no. 5 remained ventilated until the 12th postoperative day because of unstable circulation due to a perioperative myocardial infarction. However, this patient did not reveal any pathological neurologic signs. Patient no. 1 was not extubated until the 5th day after surgery because of postoperative bleeding and unstable hemodynamics. Patient no. 9 presented with slurred speech on the 1st postoperative day, but this returned to normal the next day.

When patient no. 6, who had a stroke and the highest postoperative S-100 values, is excluded, the correlations are as follows: duration of circulatory arrest versus postoperative S-100: $r_S=0.64$, n. s.; duration of circulatory arrest versus S-100 day 1: $r_S=0.83$, $P<0.05$; duration of circulatory arrest minus duration of retrograde perfusion versus postoperative S-100: $r_S=0.53$, n. s.; duration of circulatory arrest minus duration of retrograde perfusion versus S-100b day 1: $r_S=0.89$, $P<0.01$; duration of CPB versus postoperative S-100: $r_S=0.52$, n. s.; duration of CPB versus S-100 day 1: $r_S=0.05$, n. s.

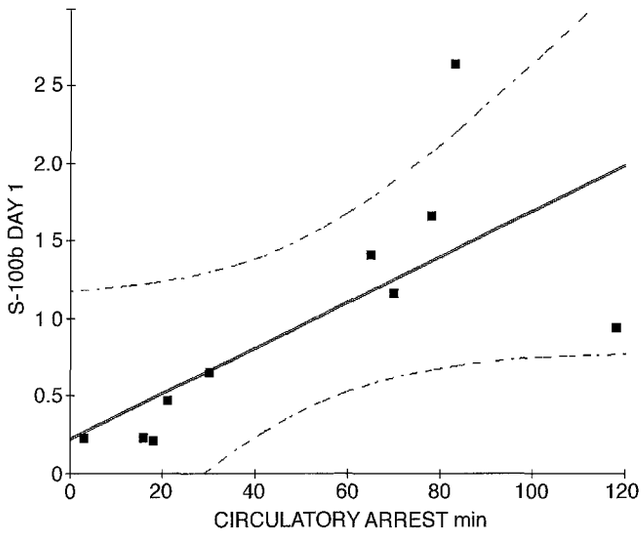

Fig. 1 Individual s-levels of S-100 before surgery. directly after CPB and on the first postoperative day in ten patients undergoing aortic surgery with a period of circulatory arrest (rs = 0.83, p>0.01)

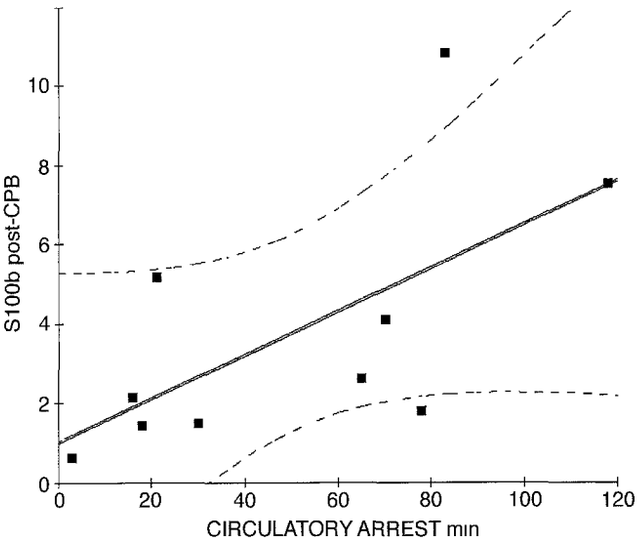

Fig. 3 Duration of circulatory arrest (min) versus serum levels of S-100 on the 1st postoperative day. Linear regression line with 2 SD variation lines (rs = 0.71 p<0 05)

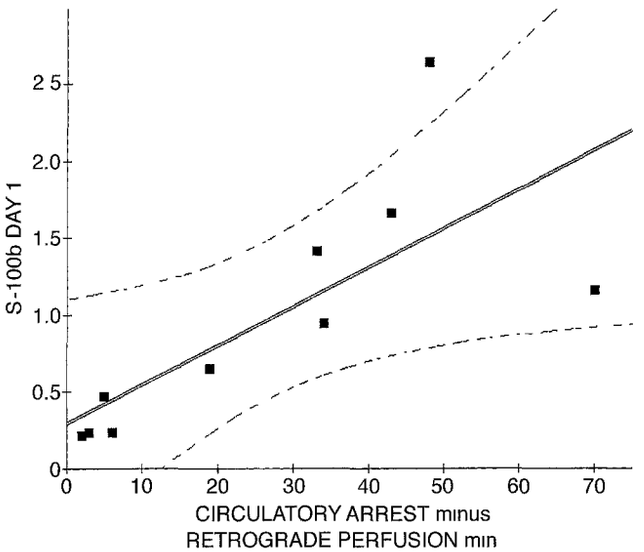

Fig. 2 Duration of circulatory arrest (min) versus serum levels of S-100 directly after CPB. Linear regression line with 2 SD variation lines (rs = 0.88. p<0.01)

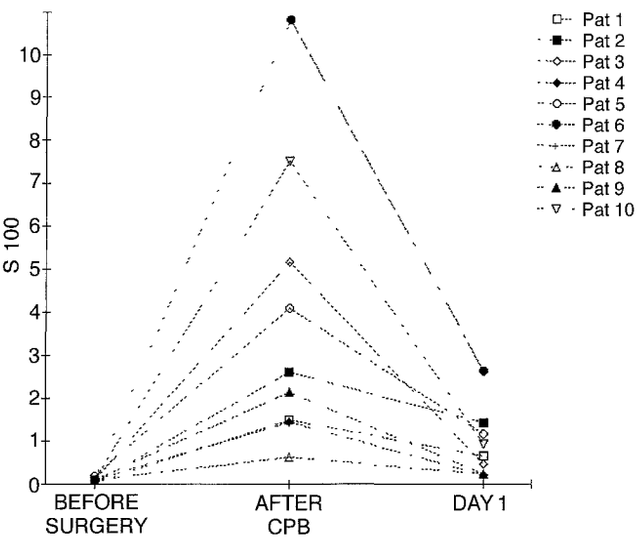

Fig. 4 Duration of circulatory arrest minus the duration of retrograde cerebral blood perfusion, i e. the duration without any cerebral perfusion versus serum levels of S-100, on the 1st postoperative day. Linear regression line with 2 SD variation lines

Discussion

The major finding of this study is that serum levels of the cerebral protein S-100 are *linearly* related to the duration of circulatory arrest during aortic surgery with deep hypothermic arrest. This indicates that circulatory arrest is damaging to the brain, despite the use of deep hypothermia and partial retrograde cerebral blood perfusion.

The serum levels of S-100 before the operation were close to the serum levels of the normal adult reference population. This argues against an ongoing cerebral injury at the start of the surgical procedure. All patients had their highest serum concentrations early after CPB, followed by

a decrease in all patients on the following day. The same pattern has been reported earlier with serum levels of creatine-kinase BB in children undergoing cardiac surgery with profound hypothermia and circulatory arrest [18, 19]. However, in our study there was an almost 40-fold increase in mean serum levels of S-100 compared to a 10-fold increase of creatine-kinase BB after circulatory arrest in children, despite longer durations of absent cerebral perfusion in the latter study.

There was a significant correlation with a linear relation between serum levels of S-100 and the duration of arrest after CPB, and the highest correlations were seen on the 1s postoperative day. When the duration of retrograde cerebral perfusion was subtracted from the duration of arrest, in order to estimate the duration of absent cerebral perfusion, there was still a significant correlation between the duration of arrest and serum levels of S-100 on the 1st postoperative day. This was not the case directly after CPB. In fact, even if patient 6, with a postoperative, verified stroke, was excluded because of his embolically induced brain injury with the highest postoperative serum levels, the highest correlation between serum levels of S-100 and duration of circulatory arrest was still seen on the 1st postoperative day. This strongly suggests that the duration of circulatory arrest, with absent cerebral perfusion, has a lasting effect on the release of S-100 from the brain, whereas other factors during or after CPB may influence the earlier post-CPB levels in a more reversible manner. S-100 levels have been reported to be related to the size of cerebral infarction [3] and it has recently been demonstrated that there is a relationship between serum levels of S-100 and the prognosis of minor head injury [11].

The duration of extracorporeal perfusion is known to be related to microembolization of the brain [6]. The lack of a significant correlation between duration of CPB and serum levels of S-100 in our study may be explained not only by the probably greater impact of circulatory arrest on the serum levels of S-100, but also by the fact that there was a much wider range in duration of circulatory arrest than in duration of CPB. Thus, we do not exclude that the duration of CPB per se may influence serum levels of S-100.

The high levels of S-100 directly after CPB and on the 1st postoperative day suggest that surgical, anesthetic and perfusion techniques may need to be improved during these operations. Earlier clinical reports showed a considerably lower cerebral perfusion early after profound hypothermic procedures with circulatory arrest in comparison with before the procedure [12, 21]. Also, anterior fontanel pressure measurements and transcranial Doppler studies have revealed an increased intracranial cerebral pressure with absent diastolic perfusion early after arrest procedures, indicating brain edema [2, 7]. This is compatible with the finding of very low oxygen saturation in jugular vein blood and release of lactate from the brain after these procedures [26]. All these data indicate brain injury with a disturbed balance between cerebral oxygen supply and cerebral oxygen demand. However, in children a limited period of circulatory arrest did not lead to higher peak values of creatine-kinase BB than when a period of continuous low pump flow was used [19]. This indicates that other factors during and after CPB are important for the release of creatine-kinase BB [9] and possibly also for S-100.

Our data showed the highest correlations between serum levels of S-100 and circulatory arrest when the duration of retrograde cerebral perfusion had been subtracted. This suggests that circulatory arrest with absent cerebral perfusion is damaging to the brain and that retrograde cerebral blood perfusion during circulatory arrest probably protects the brain. In what way retrograde cerebral perfusion during profound hypothermia with circulatory arrest will fully compensate an arrested antegrade blood perfusion remains to be evaluated. Experimental studies have indicated that antegrade cerebral perfusion may be superior even during profound hypothermia, since antegrade cerebral perfusion, in contrast to retrograde, did not lead to a net release of lactate from the brain [8]. New experimental models including intermittent antegrade or retrograde cerebral perfusion remain to be evaluated in the clinical setting. However, a recent retrospective study of patients undergoing repair of type A aortic dissections reported fewer cases of early death due to cerebral damage with retrograde cerebral perfusion than when antegrade or no cerebral perfusion was applied during the circulatory arrest [15]. This may be explained by the high incidence of severe arteriosclerosis in this patient category and that retrograde cerebral perfusion may wash out debris and air from the arterial bed before normal antegrade perfusion is resumed.

All our patients recovered from surgery without overt neurologic injury, except one patient with a stroke. However, the occurrence of postoperative brain dysfunction is very much dependent on the sensitivity of the test [22].

In summary, S-100 serum levels after aortic surgery with deep hypothermic circulatory arrest correlate with the duration of circulatory arrest. The highest correlation was seen on the 1st postoperative day, when the duration of absent cerebral perfusion was tested versus serum levels of S-100. This indicates that the duration of absent cerebral perfusion is damaging to the brain despite the use of protective deep hypothermia and partial retrograde cerebral perfusion. S-100 appears to perform well under clinical circumstances as a sensitive and discriminate marker of neuronal injury.

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Discussion

Dr. D. Watson (*Norfolk, England*): Have you had the opportunity to look at it a little sooner than immediately after bypass because it's a predictor, but it's predicting it a little late.

Dr. Van der Linden: Yes. But on the other hand, if you can predict – the patient with the highest S-100 levels directly off the bypass was the patient with the stroke.

Dr. J. Bachet (*Suresnes, France*): Thank you very much for this presentation and its contributive message. As you may know during aortic arch surgery, we use antegrade perfusion with selective hypothermia. We only cool the brain and we keep the body at a mean temperature of about 28 °C. It has been largely demonstrated that hypothermic low-flow perfusion of the brain maintains the whole energetic components of the cells. Have you any idea, in your experience, of what the S-100b protein becomes in antegrade perfusion of the brain?

Dr. Van der Linden: No, I don't know anything about that. I think it's not proven yet that antegrade is better than retrograde cerebral perfusion, although it might very well be the case.

Dr. Bachet: In our experience, that is, in about 130 patients, it was much better clinically than deep hypothermia.

Dr. B. Walpoth (*Bern, Switzerland*): Since this test seems to be very sensitive, have you tested it in patients with brain injury and correlated it with magnetic resonance/CT scan findings or correlated with the amount of brain injury?

Dr. Van der Linden: Thank you for that question. This test has been widely used by neurologists and all papers published regarding this question show a direct correlation between the extent of a stroke and levels of S-100. The prognosis of minor head injury also correlates with S-100 levels.