*Acta Anaesthesiol Scand 2002; **46:** 384–389*
Printed in Denmark. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
0001-5172

Serum concentration of S-100 protein in assessment of cognitive dysfunction after general anesthesia in different types of surgery

U. Linstedt[1], O. Meyer[1], P. Kropp[2], A. Berkau[3], E. Tapp[1] and M. Zenz[1]
[1]*Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Bergmannsheil, Ruhr-University Bochum,* [2]*Institute of Medical Psychology and* [3]*Department of Anesthesiology and Intensive Care Medicine, Christian-Albrechts-University of Kiel, Germany*

Background: S-100 protein serum concentration (S-100) serves as a marker of cerebral ischemia in cardiac surgery, head injury and stroke. In these circumstances S-100 corresponds well with the results of neuropsychological tests. The aim of the present study was to investigate the value of S-100 and neuron specific enolase (NSE) in reflecting postoperative cognitive deficit (POCD) after general surgical procedures.
Methods: One hundred and twenty patients undergoing vascular, trauma, urological or abdominal surgery were investigated. Serum values of S-100 and NSE were determined preoperatively and 0.5, 4, 18 and 36 h postoperatively. Neuropsychological tests for detecting POCD were performed preoperatively and on day 1, 3, and 6 after the operation. A decline of more than 10% in neuropsychological test results was regarded as POCD. Furthermore, we retrospectively compared the S-100 in patients with and without POCD in different types of surgery.
Results: **According to our definition, forty**-eight patients had POCD (95% confidence interval: 37.5–58.5). These patients showed higher serum concentrations of S-100 (median 024 ng/ml; range 0.01–3.3 ng/ml) compared with those without POCD (n=69; median 0.14 ng/ml; range 0–1.34 ng/ml) 30 min postoperatively (P=0.01). Neuron specific enolase was unchanged during the course of the study. Differences of S-100 in patients with and without POCD were found in abdominal and vascular surgery but not in urological surgery.
Conclusion: When all patients are pooled, S-100 appears to be suitable in the assessment of incidence, course and outcome of cognitive deficits. We suspect that in some surgical procedures, such as urological surgery, S-100 appears to be of limited value in detecting POCD. Neuron specific enolase did not reflect neuropsychological dysfunction after noncardiac surgery.

Received 21 May 2000, accepted for publication 6 November 2001

Key words: postoperative cognitive deficit; serum markers; S-100; NSE.

Serum markers of cerebral damage, such as S-100 protein and neuron specific enolase (NSE), are increasingly used in diagnosis and prognosis of cognitive function after cardiac surgery (1–6), head injury (7, 8), resuscitation (9, 10) and stroke (11). In these circumstances, structural brain damage may occur as a result of cerebral embolism, ischemia, and increased intracranial pressure. In less severe cases, the leading symptoms are cognitive deficits. After noncardiac surgery, postoperative cognitive deficiency (POCD) may also develop. Postoperative cognitive deficiency occurs in various frequencies, depending on factors such as age and type of surgery (12). Structural brain damage has rarely been found (12). The present study was undertaken to investigate S-100 and NSE as markers of cognitive deficit in noncardiac surgery.

S-100 is an acidic calcium-binding protein, first isolated from central nervous tissue in 1965 (13). It is found in astrocytes and Schwann cells. Neuron specific enolase is an isoenzyme of the glycolytic enzyme enolase, and is found in the zytoplasma of neurons and cells of neuro-endocrine differentiation. Normal serum concentrations are low, and serum concentrations are increased after damage to central nervous cells as well as blood–brain barrier dysfunction.

A correlation between neuropsychological function and the serum level of S-100 was found in patients either with traumatic head injury (7, 8) after cardiac surgery (1–6) or stroke (11), respectively.

The ISPOCD study group found significantly higher S-100 levels in patients with POCD (14). High incidences of POCD are described in patients undergoing

hip or knee arthroplasty (15–17). Nevertheless, there was no correlation between serum concentration of S-100 and neuropsychological outcome: both patients with and without POCD showed a significant increase of S-100 serum concentrations postoperatively (18).

The purpose of the present study was to investigate the relationship of increasing S-100 and NSE serum concentrations after general anesthesia and the occurrence of POCD. Furthermore, this relationship was retrospectively analyzed in different types of surgery.

Methods

One hundred and twenty patients, scheduled for elective abdominal, vascular, urological (no transurethral resection of prostate) or trauma surgery (exclusive of hip or knee joint replacement), were investigated. The study was approved by the institutional Ethics Committee and the patients gave their informed consent. Exclusion criteria were ASA risk classification >3, persistent neurological deficits as a result of stroke, psychiatric diseases, including severe dementia, deafness, impaired vision, and neuropsychological test results of <70% of standard values.

Following premedication with 3.75–7.5 mg midazolam orally, anesthesia was induced with fentanyl 0.1 mg, etomidate 0.25 mg/kg b.m. and succinylcholine 1.5 mg/kg b.m. The patients were intubated, and anesthesia was maintained with isoflurane (end-tidal concentration 0.5–0.8%) and oxygen/nitrous oxide(35/65%) in a semiclosed circuit anesthetic system. Monitoring consisted of pulse oxymetry, oscillometric blood pressure measurement and 3-channel-electrocardiography.

The serum levels of S-100 and NSE were determined before induction of anesthesia and 30 min, 4 h, 18 h, and 36 h after the end of anesthesia. Normal values assumed for S-100 were ≤0.12 ng/ml (luminescence immunoassay, Sangtec 100 LIA-mat®, Byk Sangtec, Germany) and for NSE ≤12.0 ng/ml (radioimmunoassay).

The neuropsychological performance of patients was tested one day before surgery, and on day 1, 3, and 6 after the operation. Testing was performed by a clinical psychologist in a quiet room. The Digit-Symbol-Substitution Test (DSS) of the Wechsler Adult Intelligence Scale (19) was used as a measure of attention. The DSS indicates aspects of general psychomotor and perceptual speed, divided attention, associative memory and visuo-motor coordination. The number of correct symbols used was according to correction for age.

Sustained attention and visual scanning ability under time pressure was assessed by the 'Concentration Endurance Test d2' (20, 22). The total number of scanned targets, minus the errors, was analyzed.

Cognitive processing speed as an expression of intellectual ability was determined by the 'number connection test' (21). Subjects had to connect numbers in ascending order under time pressure.

The neuropsychological examination was evaluated using standard values corrected for age (SV; mean: 100, standard deviation: 10).

Statistical analysis

Statistical procedures included multiple measure ANOVA for comparison of S-100, NSE serum concentrations and neuropsychological test results during investigation. Because of non-normal distribution of S-100 and NSE, these values were expressed as median and range, and the Mann–Whitney *U*-test was used for comparison of S-100 and NSE values in patients with and without POCD (SPSS, version 9.0). Sequential testing results were corrected according to Bonferroni. Age dependency of S-100 and NSE was tested by Spearman's rank correlation.

Table 1

Demographic data of the patients, presented as median (range), and numbers of surgical procedures.

	Abdominal surgery	Urological surgery	Trauma surgery	Vascular surgery	All patients
n	46	39	19	16	120
Age (years)	62 (27–85)	65 (19–78)	42 (18–72)	66(47–76)	64 (18–85)
Duration of anesthesia (min)	180 (90–480)	189 (127–670)	237 (110–360)	225 (105–395)	190 (90–670)
Duration of surgery (min)	148 (55–485)	135 (93–605)	195 (20–305)	172 (75–350)	154 (20–605)
Surgical procedures	Liver (6) Bowel (15) Hernia (5) Biliary (9) Stomach (4) Others (7)	Prostatic (28) Renal (11)	Osteosynthesis (13) Arthroscopy (2) Others (4)	Abdominal aortic (6) Peripheral vascular (10)	

Results

Demographic data of patients are shown in Table 1. Three patients were excluded because of necessity of postoperative ventilation. Forty-eight patients (41%, 95% CI: 37.5–58.5) had POCD during the week after surgery. For the number of patients with POCD at different time points in the investigation and for the number of tests with >10% decline, see Table 2.

The distribution of frequency of POCD was similar in all specialties, except for trauma surgery where only two patients suffered from POCD (10.5%) (Table 3).

S-100

Preoperatively, median S-100 serum-concentration was 0.02 ng/ml (range 0–0.2). There was no age-dependency ($P=0.55$). All study patients with POCD had significantly higher postoperative S-100 levels compared with those without POCD (Table 4, Fig. 1: 'all patients'). However, patients without POCD also showed postoperative increase in S-100 ($P<0.01$).

After vascular surgical procedures, maximum serum concentrations occurred 30 min postoperatively: median=0.65 ng/ml (range 0.01–1.57) in the presence of POCD (n=9), and 0.21 ng/ml (0.02–0.29) without POCD (n=7) (Fig. 1).

After abdominal surgery, the maximum S-100 in patients with POCD (n=21) was 0.21 ng/ml (median range: 0.01–2.07) compared with 0.1 ng/ml (median range: 0–0.86) in patients without POCD (n=25).

In our urological surgery (Fig. 1), patients with POCD (n=16) showed maximum S-100 levels of 0.22 ng/ml (0.02–0.05), and in those without POCD (n=21) S-100 was 0.14 (0–1.1).

In our trauma surgery the number of patients with POCD (n=2) was not sufficient for analysis.

Neuron specific enolase

In preoperative NSE values there was no age-dependency ($P=0.39$). There is no median increase in NSE serum concentration postoperatively. Values of patients with and without POCD, respectively, did not differ significantly (Table 5). Furthermore, the NSE values did not differ between the surgical specialties

Table 2

Number of patients investigated at day 1, 3 and 6, postoperatively. and patients with >10% decline in 1, 2 and 3 neuropsychological tests of the test battery (= POCD), on day 1, 3 and 6, postoperatively. Missing values on day 3 and 6 result from patients being discharged before testing.

Postoperatively:	1st day	3rd day	6th day
All patients investigated	117	108	83
>10% decline in 1 test	21	11	8
>10% decline in 2 tests	8	3	4
>10% decline in 3 tests	12	7	0

Table 3

Numbers of patients with and without postoperative cognitive deficit in different types of surgery. Postoperative cognitive deficit was assumed with a ≥10% decline in neuropsychological test results, postoperatively.

	Abdominal surgery	Urological surgery	Trauma surgery	Vascular surgery	Summary
POCD	21	16	2	9	48 (41%)
No POCD	25	21	17	7	69 (52%)
	46	37	19	16	117

POCD, postoperative cognitive deficit.
Chi-squared statistics: $P=0.03$.

Discussion

S-100 appears to be a suitable marker of POCD when all patients are pooled. The group of patients with cognitive decline showed significantly higher peak S-100 values postoperatively. Elevated S-100 levels were of short duration, even in patients with POCD on day 3 and 6 after the operation. The median S-100 returned to normal within 18 h.

Several authors were able to demonstrate a relationship between the degree of neuropsychological dysfunction and S-100. This was found by Martens *et al*. (9) and Rosen *et al*. (10) after resuscitation, as did Wunderlich (11) in stroke patients. McKeating *et al*. (8) and Herrmann *et al*. (7) found a relationship between S-100 and the degree and outcome of severe head injury.

The majority of S-100 studies were related to cardiac surgery and cardiopulmonary bypass (CPB). These investigations confirm the value of S-100 in assessment of POCD. In light of the pathophysiology of POCD after cardiac surgery it is interesting that after minimal-invasive procedures (off-pump surgery) with lower amounts of cerebral emboli, the increase of S-100 is reduced compared with conventional CPB (1).

In our study, NSE remained unchanged in both patients with and without POCD. This finding was confirmed by others in noncardiac surgery (14, 18). In cardiac surgery, NSE corresponds with the degree of cognitive impairment (4–6). It is likely that NSE does not reflect minor neuropsychological dysfunction (18).

It was also found in the present study that S-100 was elevated also in patients without POCD. This finding is in accordance with other investigations: S-100 levels increase in almost all patients for hip or knee arthroplasty (mean: 1.03 ng/ml, range 0.18–3.65) (18). Rasmuss-

Table 4

S-100 serum concentrations (ng/ml) pre- and postoperatively in patients with postoperative cognitive deficit (POCD) compared with those without POCD, expressed as median (range). Results are presented patients in general surgery, urology, trauma and vascular surgery, respectively. Postoperatively S100 concentrations were increased significantly in both groups at all time points.

	n	Pre*	30 min post*	4 h post*	18 h post*	36 h post*
POCD	48	0.02 (0–0.18)	0.25 (0.01–3.3)	0.17 (0.01–2.07)	0.1 (0–1.79)	0.07 (0.01–0.57)
no POCD	69	0.02 (0–0.2)	0.14 (0–1.34)	0.08 (0–0.86)	0.06 (0–0.46)	0.04 (0–0.47)
P†		0.81	0.01	0.001	0.002	0.005

POCD, postoperative cognitive deficit.
*Operatively.
†Level of significance between 'POCD' and 'no POCD'.

Table 5

Neuron specific enolase (NSE) serum concentrations (ng/ml) pre- and postoperatively in patients with postoperative cognitive deficit (POCD) compared with those without POCD, expressed as median (range). Significant differences were found neither between 'POCD' and 'no POCD' nor between NSE pre- and postoperatively.

	n	Pre*	30 min post*	4 h post*	18 h post*	36 h post*
POCD	48	6.1 (3.7–10.1)	5.7 (3.6–34.6)	6.4 (3.8–11.2)	6.8 (3.5–51.7)	5.5 (3.4–11.7)
No POCD	69	6.3 (3–94.2)	5.7 (2.9–42.9)	6.4 (0–42.6)	6.1 (3.1–27.7)	5.8 (3.4–74.3)
P†		0.09	0.46	0.19	0.11	0.1

POCD, postoperative cognitive deficit.
*Operatively.
†Level of significance between 'POCD' and 'no POCD'.

en and the ISPOCD group found S-100 and NSE serum levels in patients after abdominal surgery comparable to our study results. The mean of S-100 in patients without POCD on the first postoperative day was 0.3 ng/ml, representing a 3.5-fold increase. Neuron specific enolase levels were constant (14). The explanation for the S-100 release as a short-lasting glial-cell dysfunction is unsatisfying. So far, there is no evidence of structural damage of glial cells and dysfunction of blood–brain barrier during uncomplicated anesthesia, preceding the release of S-100 from glial cells into peripheral blood. Furthermore, NSE and neuropsychological testing was normal in these patients. Neuron specific enolase appears to be released only in cases of severe brain damage, such as stroke (11), after resuscitation (9) or neurologically complicated surgery (5).

The three tests used assessed only some topics of cognitive function, especially attentional processes. These tests have been chosen because attention plays a major role in daily behavior, and affects learning and memory as well as other aspects of cognition (22). Furthermore, with a short test battery it was easier to maintain compliance of patients, especially those of increased age and with severe POCD, respectively (23). For more comprehensive determination of POCD it is necessary to include learning and memory tasks in the test battery (22– 24).

In the present study, postoperative decline of at least

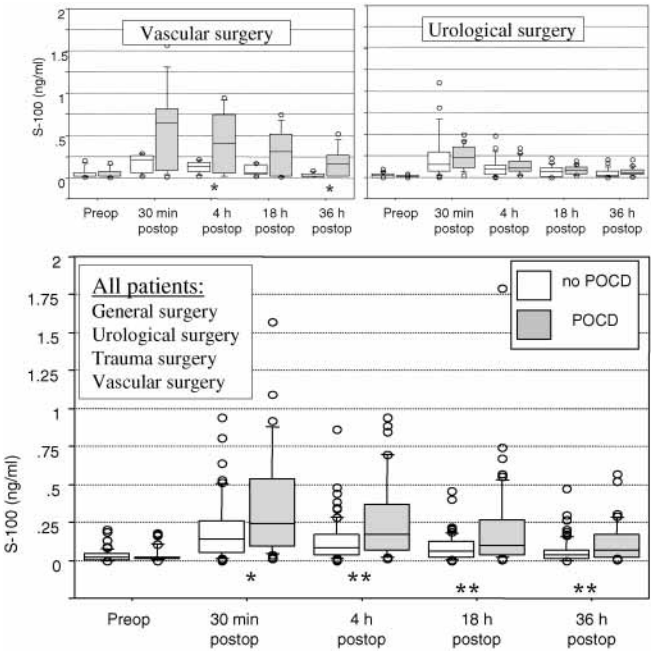

*Fig. 1 S-100 protein serum concentrations (S-100) pre- and postoperatively (30 min, 4, 18, 36 h). The main graph shows results of all patients. Inlets present data of vascular and urology patients. Data presented as box-and-whiskers-plots: boxes illustrate the 25th and 75th percentiles divided by the median; the endpoints of the whiskers illustrate the 10th and 90th percentiles; and cases outside the 10th or 90th percentiles are shown as open circles (○). Postoperatively, S-100 levels were elevated in patients with and without postoperative cognitive deficit (POCD, P<0.001). *P<0.05, **P<0.01: significant differences between patients both with and without POCD.*

one test of >1SD (10%) compared with preoperative values was defined as POCD. Approximately half the patients with POCD had a deterioration in one test only. Because standard values were used, the mean of normal controls=100, and SD=10. Therefore, a decline of 10% or more in test results indicates a deterioration of more than 1SD (approximately: z-score >1). In 'A Compendium of Neuropsychological Tests', a score of lower than 1–2SD below the mean is considered 'borderline abnormal' (22). If such deterioration of test results is attributed to POCD, this will lead to a high rate as in the present study (41% of patients). This may be of minor relevance in most of the subjects. Despite these limitations, the test battery used seems to be suitable in showing a correlation between higher median S-100 values and the presence of POCD.

A different increase in S-100 serum concentrations in different surgical specialties belongs to the findings of the present study. Patients who had vascular and abdominal surgery showed higher S-100 than patients with POCD compared with those without POCD. After urological surgery there were no differences of S-100 in patients with and without POCD, respectively. The reason for this remains unclear, and the number of patients is not sufficient for statistical power. Other investigations also found uncertainty in correlating POCD or brain damage with increased S-100 levels. After hip and knee arthroplasty increased S-100 serum levels were found in both patients with and without POCD. Neuron specific enolase remained within normal range (18). Another investigation showed constantly low S-100 levels in uncomplicated carotid thrombendarterectomy but increased concentrations after aortic surgery (26). A recent study in 100 patients scheduled for carotid endarterectomy describes an increase of S-100 in patients with uneventful outcomes ranging from 0.1 to 0.18 ng/ml. Surprisingly, patients with postoperative stroke (n=3) showed a maximum S-100 of only 0.22 ng/ml (27): these values correspond with our patients without POCD.

Most studies mentioned above assume that S-100 is released from cerebral tissues only. Therefore, increasing S-100 levels may occur after global cerebral ischemia, head injury, or cerebral embolism by cardiopulmonary bypass. It is also true that patients with POCD had mostly higher S-100 levels, but remarkable increase of S-100 in patients without POCD is difficult to explain. To date, it is not possible to define a cut-off level for S-100.

One possible explanation of elevated S-100, regardless of POCD or neurological disturbance, is an extracerebral contamination from other sources. S-100 has been regarded as highly brain specific. Values found in the brain cortex are at least fourfold those of other tissues (4, 28). But S-100 has also been found in many other tissues under physiological and pathological conditions (7), such as fat, skin, muscle (4, 28) or in metastatic melanoma (29). S-100 expression is equally induced in patients treated with β-adrenergic agonists or phosphodiesterase inhibitors (7).

In our opinion, S-100 serum concentration is of limited value in the assessment of incidence, course and outcome of postoperative cognitive deficits. Because of the weak specificity and the wide range in normal patients, postoperatively it is difficult to obtain such information in individual patients. Where there is any evidence, in the comparison of groups of patients, e.g. in vascular surgery, general surgery or cardiac surgery (1–4), for a correlation of cognitive function and S-100 levels postoperatively. After some surgical procedures, such as carotid endarterectomy (26, 27) hip or knee arthroplasty (18) or urological surgery, S-100 appears to be of no value in detecting POCD or stroke.

Acknowledgement

This work is attributed to the Department of Anesthesiology and Intensive Care Medicine, Christian-Albrechts-University of Kiel, Germany.

References

1. Anderson RE, Hansson LO, Vaage J. Release of S100B during coronary artery bypass grafting is reduced by off-pump surgery. *Ann Thorac Surg* 1999: **67**: 1721–1725.
2. Blomquist S, Johnssohn P, Lührs C et al. The appearance of S-100 protein in serum during and immediately after cardiopulmonary bypass surgery: a possible marker for cerebral injury. *J Cardiothorac Vasc Anesth* 1997: **11**: 699–703.
3. Grocott HP, Croughwell ND, Amory DW, Whithe WD, Kirchner JL, Newman MF. Cerebral emboli and serum S100β during cardiac operations. *Ann Thorac Surg* 1998: **65**: 1645–1650.
4. Johnsson P. Markers of cerebral ischemia after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996: **10**: 120–126.
5. Johnsson P, Lundquist C, Lindgren A, Ferencz I, Alling C, Stahl E. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. *J Cardiothorac Vasc Anaesth* 1995: **9**: 694–699.
6. Rasmussen LS, Christiansen M, Hansen PB, Moller JT. Do blood levels of neuron specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass? *Acta Anaesthesiol Scand* 1999: **43**: 495–500.
7. Herrmann M, Curio N, Jost S, Wunderlich MT, Synowitz H, Wallesch CW. Protein S-100 and Neuron Specific Enolase as early neurobiochemical markers of the severity of traumatic brain injury. *Restor Neurol Neurosci* 1999: **14**: 109–114.
8. McKeating EG, Andrews PJD, Mascia L. Relationship of neuron specific enolase and protein S-100 concentrations in

systemic and jugular venous serum to injury severity and outcome after traumatic brain injury. *Acta Neurochir* 1998: **71** (Suppl.): 117–119.
9. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron specific enolase for prediction of regaining consciousness after global cerebral ischemia. *Stroke* 1998: **29**: 2363–2366.
10. Rosén H, Rosengren L, Herlitz J, Blomstrad C. Increased serum levels of the S-100 protein are associated with hypoxic brain damage after cardiac arrest. *Stroke* 1998: **29**: 473–477.
11. Wunderlich MT, Ebert AD, Kratz T, Goertler M, Jost S, Herrmann M. Early neurobehavioral outcome after stroke is related to release of neurobiochemical markers of brain damage. *Stroke* 1999: **30**: 1190–1195.
12. O'Keefe ST, Ní Chonchunhair Á. Postoperative delirium in the elderly. *Br J Anaesth* 1994: **73**: 673–687.
13. Moore BA. A soluble protein characteristic of the nervous system. *Biochem Biophys Res Commun* 1965: **19**: 739–744.
14. Rasmussen LS, Christiansen M, Rasmussen H, Kristensen PA, Moller JT, and the ISPOCD group. Do blood concentration of neurone specific enolase and S-100β protein reflect cognitive dysfunction after abdominal surgery? *Br J Anaesth* 2000: **84**: 242–244.
15. Berggren D, Gustafson Y, Erikson B et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth Analg* 1987: **66**: 497–504.
16. Gustafson G, Brannstrom B, Berggren D. A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J Am Geriatr Soc* 1991: **39**: 655–662.
17. Rogers MP, Lang MH, Daltroy LH et al. Delirium after elective orthopedic surgery. *Int J Psychiatr Med* 1989: **19**: 109–121.
18. Linstedt U, Kropp P, Möller C, Zenz M. Diagnostischer Wert des S-100 Proteins und der Neuronenspezifischen Enolase als Serummarker zerebraler Störungen nach Allgemeinnarkosen. *Anaesthesist* 2000: **49**: 887–892.
19. Wechsler D. Wechsler Adult Intelligence Scale (WAIS-R). Göttingen, Hogrefe, 1981.
20. Brickenkamp R. Test d2: Aufmerksamkeits-Belastungs-Test Manual. Göttingen, Hogrefe, 1994.
21. Oswald WD, Roth E. Der Zahlen-Verbindungs-Test (ZVT). Goettingen, Hogrefe, 1997.
22. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests*. Oxford: Oxford University Press, 1998: p. 232.
23. Borowicz LM, Goldsborough MA, Selnes OA, McKhann GM. Neuropsychologic change after cardiac surgery: a critical review. *J Cardiothorac Vasc Anesth* 1997: **10**: 105–112.
24. Rasmussen LS, Larsen K, Houx P et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001: **45**: 275–289.
25. Newman S, Smith P, Treasure T et al. Acute neuropsychological consequences of coronary artery bypass surgery. *Curr Psychol Res Rev* 1987: **6**: 115–124.
26. Rasmussen LS, Christiansen MC, Johnsen J, Grönholdt ML, Moller JT. Subtle brain damage cannot be detected by measuring neuron-specific-enolase and S-100β Protein after carotid artery surgery. *J Cardiothorac Vasc Anesth* 2000: **14**: 166–170.
27. Godet G, Watremez C, Beaudeux JL, Meersschaert K, Koskas F, Coriat P. S-100β Protein levels do not correlate with stroke in patients undergoing carotid endarterectomy under general anesthesia. 2001: 15: 25–28.
28. Urdal P, Urdal K, Strömme J. Cytoplasmatic creatine cinase isoencymes in tissue obtained at surgery. *Clin Chem* 1983: **210**: 310–313.
29. Hauschild A, Engel G, Brenner W et al. S100B protein detection in serum is a significant prognostic factor in metastatic melanoma. *Oncology* 1999: **56**: 338–344.

Address:
Dr. Ulf Linstedt
Klinik für Anaesthesiologie
Intensiv Medizin- und Schmerztherapie
Knappschaftskrankenhaus
Bochum-Langendreer
Ruhr Universität Bochum
In der Schornau 23-25
D−44892 Bochum
Germany
e-mail: linstedt@anesthesia.de