Available online at www.sciencedirect.com
ScienceDirect
General Hospital Psychiatry 28 (2006) 418–423
General Hospital Psychiatry

The role of oxidative stress in postoperative delirium

Rifat Karlidag, M.D.[a,*], Suheyla Unal, M.D.[a], Ozlem H. Sezer, M.D.[a], Aysun Bay Karabulut, Ph.D.[b], Bektaş Battaloğlu, M.D.[c], Abdülkadir But, M.D.[d], Cemal Ozcan, M.D.[e]

[a]*Psychiatry Department, Inonu University Medical Faculty, Turgut Ozal Medical Center, Research Hospital, 44090 Malatya, Turkey*
[b]*Biochemistry Department, Inonu University Medical Faculty, Turgut Ozal Medical Center, Research Hospital, 44090 Malatya, Turkey*
[c]*Cardiovascular Surgery Department, Inonu University Medical Faculty, Turgut Ozal Medical Center, Research Hospital, 44090 Malatya, Turkey*
[d]*Anesthesiology Department, Inonu University Medical Faculty, Turgut Ozal Medical Center, Research Hospital, 44090 Malatya, Turkey*
[e]*Neurology Department, Inonu University Medical Faculty, Turgut Ozal Medical Center, Research Hospital, 44090 Malatya, Turkey*

Received 22 July 2005; accepted 14 June 2006

Abstract

Aim: This study aimed to determine a marker that predicts delirium using preoperative oxidative processes in patients undergoing cardiopulmonary bypass surgery.
Method: Twelve of the 50 patients included in the study showed signs of delirium during postoperative follow-up. The Delirium Rating Scale was used in patients with delirium according to *DSM-IV-TR* in the postoperative period. Venous blood samples were obtained from the patients the day before and the day after the surgery to determine plasma antioxidant enzyme levels.
Results: While there were no differences in preoperative superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels in both groups, catalase (CAT) levels were significantly lower in the delirium group. Postoperative SOD and MDA levels were also higher in the delirium group, while the GSH-Px levels were found to be lower when compared with those during the preoperative period. In the nondelirium group, the postoperative MDA and GSH-Px levels were found to be lower than preoperative levels, and postoperative SOD levels were found to be higher than preoperative levels. CAT levels were lower in the delirium group when the pre- and postoperative levels were compared in both groups. The postoperative levels of SOD, GSH-Px and CAT in the nondelirium group and MDA in the delirium group were significantly higher than preoperative levels.
Conclusion: Patients with low preoperative CAT levels appeared to be more susceptible to delirium than patients with higher CAT levels.

Keywords: Free radicals; Cardiopulmonary bypass surgery; Antioxidant enzymes; Delirium

1. Introduction

Postoperative delirium is a frequent complication of cardiopulmonary bypass (CPB) surgery. According to *DSM-IV-TR* [1], delirium is defined as a transient mental syndrome of acute onset, characterized by global impairment of cognitive functions, a reduced level of consciousness, attention abnormalities, increased or decreased psychomotor activity and a disordered sleep–wake cycle.

Although the cause of delirium after cardiac surgery is unclear, some mechanisms have been proposed. The brain may be injured by microembolism [2–7], reduced cerebral perfusion/oxygenation [8,9] and imbalance of the noradrenergic/cholinergic neurotransmission [10]. Another potential mechanism for delirium in this condition is the fact that an alteration in the tryptophan-to-phenylalanine ratio may result in serotonin excess or deficiency. High levels of phenylalanine (common in postoperative catabolic states) and low tryptophan-to-phenylalanine ratios have been associated with delirium [11]. The other possible causes for delirium after CPB may be preoperative deficits in neuropsychological function and low antioxidant levels.

CPB surgery has been shown to induce systemic inflammatory response [12] such as complement activation, endotoxin release, leukocyte activation, the expression of adhesion molecules and the release of many inflammatory mediators including oxygen free radicals [13], arachidonic

* Corresponding author. Tel.: +90 422 341 07 87; fax: +90 422 341 07 88.
E-mail address: sunal@inonu.edu.tr (S. Unal).

0163-8343/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.genhosppsych.2006.06.002

acid metabolites, cytokines [14,15], platelet-activating factor, nitric oxide and endothelins. This inflammatory cascade may contribute to the end-organ damage seen after cardiovascular operations [16]. Increased free-radical-induced oxidative stress together with a gradual appearance of antioxidative defense system during and after CPB by measuring F(2)-isoprostanes and alpha- and gamma-tocopherol has been shown [17]. The brain is a target for free radical damage because it has a large lipid content of myelin sheaths, a high rate of brain oxidative metabolism and a low antioxidant capacity. The cerebral tissue is therefore threatened by the increased formation of free radicals and their metabolites such as hydrogen peroxide and superoxide radicals [18,19]. To help protect against these destructive effects of free radicals, the organism produces protective antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px). Whereas SOD catalyzes the reaction of the superoxide anion to hydrogen peroxide, CAT and GSH-Px catalyze the breakdown of peroxides [20]. Particularly in erythrocytes, this appears to be the main and preferred mechanism over catalysis. It has been known that malondialdehyde (MDA), the last oxidative product of unsaturated fatty acids [21,22], and SOD values increase during reperfusion [21,23].

The antioxidant enzyme status of the tissue is important for the primary endogenous defense against free-radical-induced injury [24]. The weak antioxidant defense mechanisms may be preoperatively leading to inadequate compensation of stress appearing in various mechanisms in patients during CPB or to the inappropriate activation of antioxidants. The fact that neurons are very sensitive to oxidative stress and such conditions can lead to their death or apoptosis.

Active oxygen species are highly reactive and very short lived and are therefore difficult to measure directly [25]. For this reason, most methodologies involve indirect determinations of antioxidants and the extent of oxidative stress that an organ has been submitted. The use of peripheral markers of oxidative stress could provide a tool that may be useful to define the role of oxidative stress in several pathological conditions of the brain [26]. Kramer et al. [27] investigated whether biochemical changes that occur in rat brain tissue are also reflected in the erythrocytes. They found partial parallelism between changes in cerebral cortex homogenate and erythrocytes after complete brain ischemia.

It is proposed that even after the abolishment of dementia, cognitive sequelae and predisposition to dementia may be noted [28]. From this point of view, it is important to verify the predisposing variables and preventive means for delirium. In this study, we aimed to verify an indicator related to oxidative process that could predict delirium preoperatively. Peripheral blood samples have been used to obtain information on the altered balance between the production of free radicals and the antioxidant capacity [21].

2. Materials and methods

2.1. Patient selection

The study was carried out on patients admitted for CPB surgery to our Cardiovascular Surgery Clinic between February 2003 and December 2003. The approval of the Ethics Committee was obtained. A total of 50 consecutive patients (13 females; 37 males) who did not have dementia, who did not suffer from any systemic disease except hypertension or coronary artery disease and who had not smoked for at least 7 days before surgery were included into the study. All subjects were informed about the aims of the study during the first interview, and written consent was obtained from each of them. All patients underwent CPB.

2.2. Diagnosis of postoperative delirium

All patients were evaluated by two experienced psychiatrists on the day before surgery (OS and RK). The sociodemographic data form was completed, and the Mini Mental State Examination (MMSE) was administered. The MMSE was repeated on the fifth postoperative day by the same psychiatrists. The MMSE represents a brief, standardized method by which to grade cognitive mental status [25]. It assesses orientation, attention, immediate and short-term recall, language and the ability to follow simple verbal and written commands. Furthermore, it provides a total score that places the individual on a scale of cognitive function.

The clinician visited the patients three times a day postoperatively to monitor their level of consciousness. The treatment team was trained on noticing the patient's level of consciousness and asked to inform the clinician if there was any change. Twelve of the 50 patients included in the study fulfilled the *DSM-IV-TR* diagnostic criteria for delirium during postoperative follow-up visits. Eleven of the 12 patients in the delirium group were diagnosed with delirium on the first postoperative day while one patient was diagnosed on the second day.

The Delirium Rating Scale (DRS) was used to determine the severity of the delirium. DRS was developed by Trzepacz et al. [29] and consists of 10 items. The highest possible total score is 32 points. Delirium was defined as a score of 10 points or higher, 12–17 points are accepted as mild delirium, 18–28 points are classified as moderate delirium and 29–32 points denote severe delirium. We grouped patients into those with delirium as "delirium" ($n=12$) and those without delirium as "nondelirium" ($n=38$).

2.3. Antioxidant enzyme assay method

Plasma SOD activity was measured according to Sun et al. [30] by determining the reduction of nitroblue tetrazolium (NBT) by superoxide anion produced with xanthine and xanthine oxidase. One unit of SOD is defined as the amount of protein that inhibits the rate of NBT reduction by 50%. Results were expressed as Unit/L.

Table 1
The average age, bypass duration, cross-clamp duration, amount of cardioplegia administered, partial oxygen pressure during surgery and sex of the delirium and nondelirium groups

	Delirium ($n=12$), mean±S.D.	Nondelirium ($n=38$), mean±S.D.	P
Age	63.3±10.4	58.5±10.8	NS[a]
Bypass	114.9±23.0	99.6±26.4	NS[a]
Cross clamp	89.9±21.0	71.0±25.8	<.02[a]
Cardioplegia	3254.2±935.6	2400.0±765.3	<.01[a]
pO_2	327.5±50.3	323.2±70.8	NS[a]
Sex (F/M)	5/7	8/30	NS[a]

Bypass, the total duration the heart was supported by the pump during surgery (in minutes); cross clamp, the total duration from the time the clamp was placed on the aorta to the time it was opened (in minutes); cardioplegia, the blood and potassium ringer lactate solution infused during the surgery (in milliliters); pO_2, the partial oxygen pressure during the surgery (in mmHg); NS, not significant.
[a] Mann–Whitney U.

Erythrocyte CAT activity was determined according to the method of Aebi [31] by monitoring the initial rate of disappearance of hydrogen peroxide (initial concentration, 10 mM) at 240 nm in a spectrophotometer. Results were reported as K/g Hb.

Erythrocyte MDA, referred to as thiobarbituric acid reactive substances, were measured with thiobarbituric acid at 532 nm in a spectrofluorometer as previously described [32]. Results were reported as μmol/g Hb.

Erythrocyte GSH-Px activity was measured according to Paglia and Valentine [33] by monitoring the oxidation of reduced nicotinamide adenine dinucleotid phosphate (NADPH) at 340 nm. Enzyme units were defined as the number of micromoles of NADPH oxidized per minute and calculated using the extinction coefficient of NADPH at 340 nm of 6.22×106/M/cm. Results were reported as units/g Hb.

2.4. Statistical analysis

Patients were grouped into those developing and not developing delirium for statistical evaluation. Statistical analysis of the results was carried out using the commercially available SPSS 11.0 for Windows statistical software.

Chi-square test was used to compare sex distribution between groups. The standard distribution was checked with the Kolmogorov–Smirnov test. As it was not a case of normal distribution, the Mann–Whitney U Wilcoxon test was used to compare age, MMSE values, duration of bypass, duration of cross clamp, amount of cardioplegic administered and the partial oxygen pressure during surgery between delirium and nondelirium groups. Wilcoxon test was used to compare preoperative and postoperative MMSE values in each group. All data (age, MMSE values, duration of bypass, duration of cross clamp, amount of cardioplegic administered and the partial oxygen pressure during surgery) were correlated by means of Spearman's correlation coefficient. Age, cross-clamp duration and cardioplegia variables were used as confounding factors for univariate analysis of variance, and the statistical calculations were repeated. The results were expressed as mean value±standard deviation (MV±S.D.). A P value of less than .05 was considered significant.

3. Results

Twelve of the 50 study subjects met the *DSM-IV-TR* diagnostic criteria for delirium during postoperative follow-up. Patients diagnosed with delirium had a mean score of 15.7±4.3 points (range, 12–26) on the DRS. The delirium was mild in 7 patients and moderate in 5 patients according to the scores obtained from the DRS. The MMSE values showed a statistically significant postoperative decrease compared with the preoperative period in both groups.

The average age, bypass duration, cross-clamp duration, amount of cardioplegic administered and partial oxygen pressure during surgery in the delirium and nondelirium groups are presented in Table 1.

According to the preoperative antioxidant enzyme levels, the delirium group had a CAT level significantly lower than the nondelirium group. The postoperative SOD, GSH-Px and CAT levels were significantly higher in the nondelirium group while the MDA levels were statistically significantly higher in the delirium group. In the delirium group, postoperative SOD, GSH-Px and MDA levels have been

Table 2
Comparison of the pre- and postoperative CAT, SOD, GSH-Px and MDA levels of the delirium and nondelirium groups

	Delirium ($n=12$)	Nondelirium ($n=38$)	P
CAT (K/g Hb)			
Preoperative	182.2±83.0	236.3±83.7	<.035[a]
Postoperative	149.2±67.2	265.7±73.3	<.001[a]
P	NS[b]	NS[b]	
SOD (U/L)			
Preoperative	60.3±9.9	54.8±7.3	NS[a]
Postoperative	71.7±11.7	93.7±8.3	<.001[a]
P	<.023[b]	<.001[b]	
GSH-Px (U/g Hb)			
Preoperative	3632.7±700.0	3917.2±648.3	NS[a]
Postoperative	1920.8±588.5	2921.9±814.4	<.001[a]
P	<.003[b]	<.001[b]	
MDA (μmol/g Hb)			
Preoperative	8.1±2.0	8.9±3.6	NS[a]
Postoperative	11.1±3.6	3.2±1.5	<.001[a]
P	<.011[b]	<.001[b]	

NS, not significant.
[a] Mann–Whitney U.
[b] Wilcoxon.

found to be significantly higher than preoperative levels. The mean CAT level was not statistically significantly different postoperatively compared with the preoperative values. In the comparison of the pre- and postoperative CAT, SOD, GSH-Px and MDA levels of the nondelirium group, there were statistically significant differences for SOD, GSH-Px and MDA. There were no statistically significant differences between pre- and postoperative CAT levels in both groups (Table 2).

The SOD level increased in a statistically significant manner in both groups but more markedly in the nondelirium group postoperatively when compared with the preoperative period. In contrast, the GSH-Px values had decreased postoperatively when compared with the preoperative values in a statistically significant manner in both groups, again more markedly in the nondelirium group. However, the change in the MDA level due to surgery was very different in the two groups. Although there was a statistically significant increase in the MDA level postoperatively compared with the preoperative period in the delirium group, there was a statistically significant decrease in the nondelirium group.

There was no significant difference in the results when statistical analysis was repeated after cross-clamp period and when cardioplegia-related factors were used as confounding factors for univariate analysis of variance. The same situation was true for age. The results again did not differ significantly when age was taken as a confounding factor in addition to cross-clamp period and cardioplegia.

4. Discussion

It has been known for a long time that the risk of delirium and neuropsychological deficit development is high after CPB [34–36]. We found a significant decline in the MMSE score in the postacute stage after surgery in both the delirium and nondelirium groups. Berr et al. [37,38] have shown with a series of studies that "oxidative stress and/or antioxidant deficiencies" increase damage to cerebral tissue and lead to cognitive decline with irreversible degeneration. Jackson et al. [28] have found that the common finding of nine studies on delirium and cognitive functions was cognitive decline continuing as a sequelae even after delirium.

Many etiologic mechanisms such as the acute syndromes of vasospasm, coagulopathy, microembolism [39,40], ischemia/reperfusion injury and potential harmful mediators of the inflammatory response [41,42] have been proposed for delirium. These mechanisms interrelate and produce synergistic, cumulative effects on brain function during and after the operation [43]. The interactions among these mechanisms are shown in Fig. 1.

CPB triggers an inflammatory response that can lead to the development of postoperative organ dysfunction [44]. This postoperative neuropsychological decline may significantly be associated with the postoperative release of some neurobiochemical markers of brain damage, such as protein S-100B and neuron-specific enolase [45].

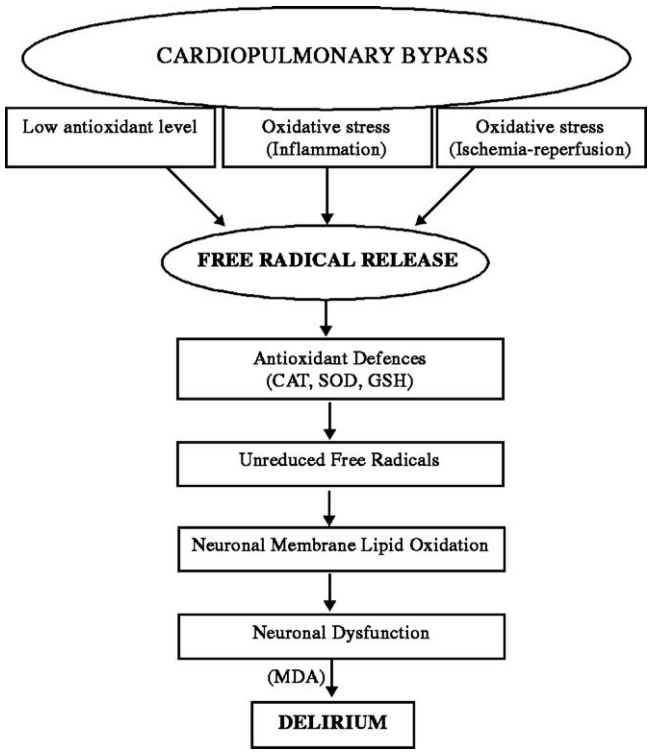

Fig. 1. Delirium development process in relation to oxidative stress in patients after CPB.

There was no significant difference in the statistical results when cross-clamp period, cardioplegia-related factors and age were taken as a confounding factor, which indicates that oxidative stress markers are important independent predictors of delirium. The brain is one of the organs most sensitive to inadequate cerebral perfusion, oxygenation and excess oxidative stress products [46–49]. Hyperoxic CPB, widely used during cardiac operations, may cause oxygenation injury induced by reactive oxygen intermediates [50]. Ulus et al. [17] showed the increase of free-radical-induced oxidative stress together with a gradual appearance of antioxidative system during and after CPB. Ischemia may impair mitochondrial SOD. During CPB, excessive ATP consumption leads to the accumulation of the purine catabolites hypoxanthine and xanthine, which, upon subsequent reperfusion and influx of oxygen, are metabolized by xanthine oxidase to yield massive amounts of superoxide and hydrogen peroxide [51]. This increased production of H_2O_2 during CPB surgery is likely to induce delirium [47,52]. The elimination of H_2O_2 is very important as hydroperoxides can initiate a lipid peroxidation chain reaction and consequently propagate free radicals, leading to DNA and membrane damage [53,54]. The half-life of free radicals is very short and repair of oxidative stress begins within a short time after they are secreted.

In the reperfusion phase, oxidative stress may release oxidized glutathione [46–48], but GSH-Px and SOD decline to the baseline level at the 24th postoperative hour [55]. We found that SOD increased more markedly in the

nondelirium group postoperatively. This indicates that oxidative damage may be compensated in this group. Full compensation cannot take place in the delirium group, thus leading to pathology. In a recent study by Matata and Galinanes [56], lipid and protein oxidation was found to be increased during CPB in patients with diabetes.

The antioxidant enzyme levels of the organism are accepted as an indication of the resistance that the tissues will show to possible oxidative stress. Inadequate response of the antioxidant mechanism provides a basis for oxidative stress to cause tissue damage. CAT activity was found to be a major determinant of cellular resistance to H_2O_2 toxicity in cell lines [57–60]. Christiansen et al. [61] have shown that the CAT −262T allele serves as protection against neurodegenerative and physical decline. We also found that the individuals with low preoperative CAT levels developed a statistically significantly higher rate of delirium. In parallel with these findings, we found higher postoperative levels of SOD, GSH-Px and CAT in the group that did not develop delirium. We also found higher levels of MDA, the last product of lipid peroxidation, in the delirium group. In contrast, MDA levels showed a significant decrease when compared with the preoperative levels in the group that did not develop delirium. Our results indicate that a low CAT capacity (low CAT levels) leads the tissues to suffer more damage from oxidative stress. The high MDA levels found in the delirium group postoperatively show that oxidative catabolism continues until the end stage in these patients and concludes with the peroxidation of unsaturated fatty acids. Although the MDA defense mechanism tries to protect the system up to a point, it may become destructive above a certain level.

This study has some strengths and limitations. Using peripheral blood samples for measuring free radicals and antioxidant capacity may not exactly reflect the central condition. The fact that DRS scores were not collected for nondelirious patients has prevented regression analyses to be carried out. On the other hand, three-times-a-day evaluation of patients has revealed a more reliable data.

Our data indicate that a low level of CAT before CPB seems to be associated with postoperative delirium. It is known that CAT protects cells from oxidative stress [62]. Antioxidants are indicators of the organism suffering from stress, but it seems that a protective system such as CAT at higher relative levels preoperatively prevents delirium progression. Determination of preoperative plasma CAT concentrations may therefore have a predictive value with respect to postoperative delirium development after CPB. If future studies indicate a CAT cutoff point for preoperative patients, it may be possible to predict patients that will become delirious after surgery, and these patients may be put on antioxidant treatment preoperatively.

Acknowledgment

This research has been supported by a research fund from Inonu University.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text rev. Washington (DC): American Psychiatric Press; 2000.
[2] Bojar RM, Najafi H, DeLaria GA, Serry C, Goldin MD. Neurological complications of coronary revascularization. Ann Thorac Surg 1983;36:427–32.
[3] Moody DM, Bell MA, Challa VR, Johnston WE, Prough DS. Brain microemboli during cardiac surgery or aortography. Ann Neurol 1990; 28:477–86.
[4] Clark RE, Brillman J, Davis DA, et al. Microemboli during CABG: genesis and effect on outcome. J Thorac Cardiovasc Surg 1995; 109:249–58.
[5] Stump DA, Rogers AT, Hammon JW, Newman SP. Cerebral emboli and cognitive outcome after cardiac surgery. J Cardiothorac Vasc Anesth 1996;10:113–9.
[6] Hammon Jr JW, Stump DA, Kon ND, et al. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. Ann Thorac Surg 1997;63:1613–8.
[7] Borger MA, Peniston CM, Weisel RD, et al. Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions. J Thorac Cardiovasc Surg 2001;121:743–9.
[8] Nollert G, Mohnle P, Tassani-Prell P, et al. Postoperative neuropsychological dysfunction and cerebral oxygenation during cardiac surgery. Thorac Cardiovasc Surg 1995;43:260–4.
[9] Gokgoz L, Gunaydin S, Sinci V, et al. Psychiatric complications of cardiac surgery postoperative delirium syndrome. Scand Cardiovasc J 1997;31:217–22.
[10] Eikelenboom P, Hoogendijk WJG. Do delirium and Alzheimer's dementia share specific pathogenetic mechanisms? Dement Geriatr Cogn Disord 1999;10:319–24.
[11] van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Habbema JD. Is delirium after cardiac surgery related to plasma amino acids and physical condition? J Neuropsychiatry Clin Neurosci 2000; 12:57–63.
[12] Smith PLC. The systemic inflammatory response to cardiopulmonary bypass and the brain. Perfusion 1996;11:196–9.
[13] Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 1999;54:B239–46.
[14] Stefano GB, Bilfinger TV. Human neutrophil and macrophage chemokinesis induced by cardiopulmonary bypass: loss of DAME and IL-1 chemotaxis. J Neuroimmunol 1993;47:189–98.
[15] Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 2003;75:S715–20.
[16] Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass. Mechanisms involved and possible therapeutic strategies. Chest 1997;112:676–92.
[17] Ulus AT, Aksoyek A, Ozkan M, et al. Oxidative stress and changes in α- and γ-tocopherol levels during coronary artery bypass grafting. Ann N Y Acad Sci 2004;1031:352–6.
[18] Choi BH. Oxygen, antioxidants and brain dysfunction. Yonsei Med J 1993;34:1–10.
[19] Metodiewa D, Koska C. Reactive oxygen species and reactive nitrogen species: relevance to cyto(neuro)toxic events and neurologic disorders. An overview. Neurotox Res 2000;1:197–233.
[20] Halliwell B, Gutteridge JMC. Free radicals in biology and medicine. 2nd ed. Oxford: Clarendon Press; 1989. p. 543.
[21] Lantos J, Temes G, Gobolos L, Jaberansari MT, Roth E. Is peripheral blood a reliable indicator of acute oxidative stress following heart ischemia and reperfusion? Med Sci Monit 2001;7: 1166–70.
[22] Kim KB, Chung HH, Kim MS, Rho JR. Changes in the antioxidative defensive system during open heart operations in humans. Ann Thorac Surg 1994;58:170–5.

[23] Vogt M, Bauer MK, Ferrari D, Schulze-Osthoff K. Oxidative stress and hypoxia/reoxygenation trigger CD95 (APO-1/Fas) ligand expression in microglial cells. FEBS Lett 1998;429:67–72.
[24] Islekel S, Islekel H, Guner G, Ozdamar N. Alterations in superoxide dismutase, glutathione peroxidase and catalase activities in experimental cerebral ischemia–reperfusion. Res Exp Med 1999;199:167–76.
[25] Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[26] Repetto MG, Reides CG, Evelson P, et al. Peripheral markers of oxidative stress in probable Alzheimer patients. Eur J Clin Invest 1999;29(7):643–9.
[27] Kramer K, Voss HP, Grimbergen JA, Timmerman H, Bast A. The effect of ischemia and recirculation, hypoxia and recovery on antioxidant factors and beta-adrenoceptor density. Is the damage in the erythrocytes a reflection of brain damage caused by complete cerebral ischemia and by hypoxia? Biochem Biophys Res Commun 1987; 149(2):568–75.
[28] Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol Rev 2004;14(2):87–98.
[29] Trzepacz P, Baker R, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;23:89–97.
[30] Sun Y, Oberley L, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem 1988;34:497–500.
[31] Aebi H. Catalase. In: Bergmeyer HU, editor. Methods in enzymatic analysis, vol 3. Weinheim: Verlag Chemie; 1982. p. 273–82.
[32] Wasowicz W, Neve J, Peretz A. Optimized steps in flourometric determination of thiobarbituric acid-reactive substances in serum: importance of extraction pH and influence of sample preservation and storage. Clin Chem 1993;39:2522–6.
[33] Paglia D, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967;70:158–69.
[34] Mahanna EP, Blumenthal JA, White WD, et al. Defining neuropsychological dysfunction after coronary artery bypass grafting. Ann Thorac Surg 1996;61:1342–7.
[35] Walzer T, Herrmann M, Wallesch CW. Neuropsychological disorders after coronary bypass surgery. J Neurol Neurosurg Psychiatry 1997;62:644–8.
[36] Raja PV, Blumenthal JA, Doraiswamy PM. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. CNS Spectr 2004;9(10):763–72.
[37] Berr C, Richard MJ, Roussel AM, Bonithon-Kopp C. Systemic oxidative stress and cognitive performance in the population-based EVA study. Etude du Vieillissement Arteriel. Free Radic Biol Med 1998;24(7–8):1202–8.
[38] Berr C, Balansard B, Arnaud J, Roussel AM, Alperovitch A. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. J Am Geriatr Soc 2000; 48(10):1285–91.
[39] Pugsley W, Klinger L, Paschalis C, et al. Microemboli and cerebral impairment during cardiac surgery. Vasc Surg 1990;24:34–43.
[40] Sylivris S, Levi C, Matalanis G, et al. Pattern and significance of cerebral microemboli during coronary artery bypass grafting. Ann Thorac Surg 1998;6:1674–8.
[41] Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 2002;97:215–52.
[42] Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–44.
[43] Taylor KM. Brain damage during cardiopulmonary bypass. Ann Thorac Surg 1998;65:S20–6 [discussion S27-8].
[44] Frass OM, Buhling F, Tager M, et al. Antioxidant and antiprotease status in peripheral blood and BAL fluid after cardiopulmonary bypass. Chest 2001;120:1599–608.
[45] Herrmann M, Ebert AD, Galazky I, et al. Neurobehavioral outcome prediction after cardiac surgery. Role of neurobiochemical markers of damage to neuronal and glial brain tissue. Stroke 2000;31:645–50.
[46] Ferrari R, Ceconi C, Curello S, et al. Oxygen free radicals and myocardial damage: protective role of thiol-containing agents. Am J Med 1991;91(3C):95S–105S.
[47] Clermont G, Vergely C, Jazayeri S, et al. Systemic free radical activation is a major event involved in myocardial oxidative stress related to cardiopulmonary bypass. Anesthesiology 2002;96:80–7.
[48] Ferrari R, Guardigli G, Mele D, et al. Oxidative stress during myocardial ischaemia and heart failure. Curr Pharm Des 2004;14: 1699–711.
[49] Matata BM, Sosnowski AW, Galinanes M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. Ann Thorac Surg 2000;69:785–91.
[50] Ihnken K, Winkler A, Schlensak C, et al. Normoxic cardiopulmonary bypass reduces oxidative myocardial damage and nitric oxide during operations in the adult. Thorac Cardiovasc Surg 1998;116:327–34.
[51] Granger DN. Role of xanthine oxidase and granulocytes in ischemia–reperfusion injury. Am J Physiol Heart Circ Physiol 1988;255: H1269–75.
[52] Busciglio J, Yankner BA. Apoptosis and increased generation of reactive oxygen species in Down's syndrome neurons in vitro. Nature 1995;378:776–9.
[53] Halliwell B, Gutteridge JM. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J 1984;219:1–14.
[54] Girotti AW. Lipid hydroperoxide generation, turnover, and effector action in biological systems. J Lipid Res 1998;39:1529–42.
[55] Luyten CR, van Overveld FJ, De Backer LA, Sadowska AM, Rodrigus IE, De Hert SG, et al. Antioxidant defence during cardiopulmonary bypass surgery. Eur J Cardiothorac Surg 2005; 7(4):611–6 [electronic publication 2005 Jan 13].
[56] Matata BM, Galinanes M. Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokine release in patients with diabetes compared with patients without diabetes: regulatory effects of exogenous nitric oxide. Thorac Cardiovasc Surg 2000;120:1–11.
[57] Yamada M, Hashinaka K, Inazawa J, Abe T. Expression of catalase and myeloperoxidase genes in hydrogen peroxide-resistant HL-60 cells. DNA Cell Biol 1991;10:735–42.
[58] Scott MD, Lubin BH, Zuo L, Kuypers FA. Erythrocyte defence against hydrogen peroxide: preeminent importance of catalase. J Lab Clin Med 1991;118:7–16.
[59] Spitz DR, Adams DT, Sherman CM, Roberts RJ. Mechanisms of cellular resistance to hydrogen peroxide, hyperoxia, and 4-hydroxy-2-nonenal toxicity: the significance of increased catalase activity in H2O2-resistant fibroblasts. Arch Biochem Biophys 1992;292:221–7.
[60] Kasugai I, Yamada M. High production of catalase in hydrogen peroxide-resistant human leukemia HL-60 cell lines. Leuk Res 1992; 16:173–9.
[61] Christiansen L, Hans H, Petersen C, Bathum L, et al. The catalase −262C/T promoter polymorphism and aging phenotypes. J Gerontol A Biol Sci Med Sci 2004;59:B886–9.
[62] Nelson CW, Wei EP, Povlishock JT, Kontos HA, Moskowitz MA. Oxygen radicals in cerebral ischemia. Am J Physiol Heart Circ Physiol 1992;263:H1356–62.