A RANDOMIZED STUDY OF THE INFLUENCE OF PERFUSION TECHNIQUE AND pH MANAGEMENT STRATEGY IN 316 PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

II. Neurologic and cognitive outcomes

This double-blind, randomized comparison of pulsatile or nonpulsatile perfusion and alpha-stat or pH-stat management during cardiopulmonary bypass was designed to assess postoperative central nervous system outcomes. *Methods:* Neurologic and cognitive testing was conducted before the operation and 7 days and 2 months after the operation in 316 patients having coronary artery bypass and in a reference cohort of 40 patients having major vascular and thoracic operations. *Results:* As detailed in part I of this study, mortality in patients having coronary bypass was 2.8%. The incidence of stroke was 2.5% and did not differ among bypass groups. Mortality was 2.5% for the major surgery cohort. The incidence of cognitive ($p = 0.003$) and either neurologic or cognitive dysfunction ($p = 0.0002$) was higher at 7 days for the coronary bypass group than for the major surgery cohort. The incidence of neurologic dysfunction remained higher ($p = 0.050$) at 2 months in the coronary bypass group. Cognitive dysfunction at 2 months was less prevalent after 90 minutes of cardiopulmonary bypass in patients managed with alpha-stat than with pH-stat strategy (27% versus 44%, $p = 0.047$). *Conclusions:* Postoperative central nervous system dysfunction is more prevalent in patients having coronary bypass than in those having major operations. Pulsatility has no effect on central nervous system outcomes, but alpha-stat management is associated with a decreased incidence of cognitive dysfunction in patients undergoing prolonged cardiopulmonary bypass. (J THORAC CARDIOVASC SURG 1995;110:349-62)

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In part because of advances in alternate therapies, the average age, incidence of concomitant disease, and degree of atherosclerotic disease in patients presenting for coronary artery bypass (CAB) surgery have been increasing significantly over the past decade.[1] In an assessment of more than 2000 patients undergoing CAB operations, advanced age was the greatest risk factor for postoperative neurologic dysfunction.[2] In addition to age, studies have demonstrated that longer duration of cardiopulmonary bypass (CPB) also increases the risk of postoperative cognitive dysfunction.[3-5] Increasingly, patient deaths have been attributed to postoperative neurologic injury. From 1970 to 1973, 8% of patients with CAB died after an adverse neurologic event; by contrast, from 1980 to 1983, 20% of postoperative deaths were attributable to neurologic injury.[6]

At the same time a high incidence of subtle neurobehavioral dysfunction has been identified. Overall, the incidence of cognitive dysfunction after CAB operations has been demonstrated to range from 24% to 79% in the postoperative period[3, 4, 7, 8] and averages 35% at post-discharge follow-up,[4, 9] with 35% of patients still having cognitive impairment 12 months after the operation.[5]

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Previous studies have demonstrated the influence of pH management strategy[10-12] and perfusion technique[13, 14] on cerebral blood flow during CPB. However, relatively few studies have assessed their impact on postoperative patient outcomes.[15-18] Accordingly, the current study was designed to determine the influence of alpha-stat or pH-stat pH management and pulsatile or nonpulsatile perfusion during CPB on postoperative neurologic and cognitive functioning in a group of patients undergoing CAB surgery.

In addition, to better define the role of exposure to CPB in the genesis of postoperative central nervous system (CNS) dysfunction, a reference cohort of patients undergoing major thoracic or abdominal aortic procedures, but not cardiac operations, termed the *noncardiac surgical cohort,* underwent identical cognitive and neurologic examinations at similar intervals.

Methods

Study objective. This is part II of a two-part study, part I appearing elsewhere in this JOURNAL.[19] The primary objective of this double-blind, randomized, clinical trial was to compare the impact of different pH management strategies and perfusion techniques during CPB on the incidence of cognitive and neurologic dysfunction in patients after CAB surgery. Secondarily, these results were compared with the incidences of CNS dysfunction in a group of patients undergoing major noncardiac operations. Study group characteristics, protocol-related inclusion and exclusion criteria, and details of pH management and perfusion technique during CPB are described in part I.[19]

Reference cohort. To more clearly identify the risk of postoperative dysfunction as related to CPB—independent of undergoing a major surgical procedure—a *noncardiac surgical cohort* of 40 patients undergoing either abdominal aortic surgery (n = 27) or thoracic surgery (n = 13) underwent the same standardized preoperative and postoperative neurologic and cognitive assessments.

Neurologic assessment. A standardized neurologic examination assessing mentation, cranial nerve function, motor power, reflexes, sensation/cerebellar function, and gait, with 14 individual elements graded on a scale from 0 to 3 for a possible total of 42 (Table I; see also Appendix I for description), was performed within 24 hours after the operation, at 7 days after the operation, and at a 2-month follow-up visit, by a qualified nurse specialist. A score of less than 3 on any of the applicable elements on baseline assessment was identified as indicating preoperative neurologic dysfunction. The criterion for defining postoperative neurologic dysfunction was a decrease from baseline of individual elements totaling 2 or more points, representing either mild decrease in performance in two areas or significant decrease in one area.

Neuropsychologic assessment. A series of cognitive tests were administered by a nurse specialist at the same times as the neurologic examination under direction of a clinical neuropsychologist (J.S.M.). Specific tests used were as follows: (1) the Digit Span and Mental Control subtests of the Weschler Memory Scale, for which scores were standardized and averaged to achieve a composite measure of concentration, (2) the Digit Symbol subtest of the Weschler Adult Intelligence Scale-Revised (a measure of psychomotor speed); (3) the Grooved Pegboard test, a measure of manual dexterity, for which the times for both hands were summed; and (4) the Verbal Paired Associates subtest of the Wechsler Memory Scale (a measure of verbal learning). Alternate forms of the Digit Span, Mental Control, and Verbal Paired Associates were used and administered in an A-B-A sequence for half the patients and a B-A-B sequence for the other half, so as to reduce practice effects across assessments.

Cognitive dysfunction. Failure to show progressive improvement in cognitive test performance over time ("learning effect") is a highly sensitive marker of minimal dysfunction and has been used by Sotaniemi, Mononen, and Hokkanen[20] to define late dysfunction after cardiac operations. To define postoperative cognitive dysfunction and to control for the learning effect, we recruited a nonhospitalized group of 41 age and gender matched volunteers (a normative control group) to undergo the same cognitive battery at similar intervals as the treatment groups. Change scores from baseline were computed for each cognitive test, and a distribution of change scores was compiled for the normative control group to provide a range of "normal" variability in change scores that was specific for each domain (test) at each point. Cutoffs for "abnormal" functioning in the study groups were operationally defined as change scores that were exceeded by 95% (39 members) of the normative control group.[21] Values used as cutoffs for defining abnormal performance among the surgically treated patients are presented in Table II. Cognitive dysfunction was defined as impaired performance within one or more of the four areas assessed.

Statistical analysis. The target sample size for this study was 304 patients undergoing CAB. The analysis was based on an anticipated adverse cognitive outcome rate of 35%, and a reduction to 20% was considered to represent a clinically significant difference. This sample size would provide 80% power at the 0.05 α level and allow for a 10% dropout rate, to compare alpha-stat versus pH-stat management and pulsatile versus nonpulsatile perfusion, provided that these two interventions did not interact.

To standardize the influence of repeated neuropsychologic testings, we included only results from patients who underwent cognitive testing at 7 days in the 2-month follow-up analysis. Cognitive testing from patients not completing any or all components of the cognitive battery were not included in the analyses of cognitive outcomes unless their performance on that portion of the testing completed was impaired relative to their baseline level of performance.

Log-linear model analysis was first performed to ensure that no interaction existed between pH management, perfusion technique, and outcome events. Outcome events were compared between treatment groups by means of the χ^2 test. Fisher's two-tailed exact test was used if the expected

Table I

Western Perioperative Neurological Scale				
				PT#____
NEUROLOGICAL ASSESSMENT SCALE SCORES				Enter scores in appropriate columns
EXAMINATION	*PREOP*	*7 DAYS*	*2 MONTHS*	*SCALE*
MENTATION LEVEL OF CONSCIOUSNESS				3 -ALERT 2-DROWSY 1-STUPOROUS 0-COMATOSE
SPEECH				3-NORMAL 2-DYSPHASIA 1-APHASIA 0-MUTE
CRANIAL NERVES VISION				3-NORMAL 2-MILD DEFICIT 1-MOD. DEFICIT 0-SEV. DEFICIT
CRANIAL NERVES				3-NORMAL 2-MILD DEFICIT 1-MOD. DEFICIT 0-SEV. DEFICIT
MOTOR RIGHT ARM LEFT ARM RIGHT LEG LEFT LEG				3-MORMAL 2-MILD WEAKNESS 1-MOD.WEAKNESS 0-SEV. WEAKNESS
CEREBELLUM/SENSATION RIGHT SIDE SEN. LEFT SIDE SEN. CEREBELLAR FUNCTION				3-NORMAL 2-MILD DEFICIT 1-MOD. DEFICIT 0-SEV. DEFICIT
REFLEXES				3-NORMAL 2-MILD DEFICIT 1-MOD. DEFICIT 0-SEV. DEFICIT
PRIMITIVE REFLEXES				3-ABSENT 2-ONE PRESENT 1-TWO PRESENT 0-ALL PRESENT
GAIT				3-NORMAL 2-MILD DEFICIT 1-MOD. DEFICIT 0-SEV. DEFICIT
TOTAL				
BASE SCORE				

Patients are assessed and scored on a scale from 0 to 3 for a total possible score of 42, preoperatively, and at 7 days and 2 months postperatively.

Table II. *Change scores* from baseline used as cutoffs to identify impairment in surgically treated patients*

	Assessment interval	
	At 7 days	*At follow-up†*
Concentration‡	95% > −1.14	95% > −1.2
Grooved Pegboard time (sec)	95% < 9	95% < 14
Digit Symbol raw score	95% > 0	95% > −2
Associate Learning raw score§	95% > −10	95% > −4

*For Grooved Pegboard test, higher scores reflect decreased performance from baseline; for all other measures, lower scores reflect decreased performance from baseline.

†Follow-up testing was conducted approximately 2 months after baseline testing.

‡Concentration score = (Mental Control Z-score + Digit Span Z-score)/2.

§Associate Learning raw score = No. easy correct + 2 (No. hard correct).

cell sizes were small. Demographic characteristics were assessed similarly for categoric variables. Two-way factorial analysis of variance was used to examine continuous variables and to confirm that pH management did not interact with perfusion technique. No adjustments were made for multiple comparisons. Logistic regression analysis was applied to examine potential risk factors for neurologic and cognitive dysfunction.

Results

A total of 316 patients undergoing CAB operations were enrolled in this study. On average, slightly more than two patients were enrolled weekly, constituting approximately 30% of all patients undergoing CAB during this period. Demographic and clinical characteristics of the 316 patients in the study and the 40 patients in the noncardiac surgical cohort are shown in Table III. Other than significantly greater numbers of women in the major surgery cohort, there were no other differences in identifiable risk factors between patients having CAB and the reference cohort. Intended treatments during CPB were achieved such that there were appropriate and significant differences in arterial pH and arterial carbon dioxide tension between pH management groups and in pulse pressure between the pulsatile and nonpulsatile groups (Table IV).

Among 316 patients enrolled, there were 9 (2.85%) in-hospital deaths, 4 occurring in the alpha-stat group and 5 in pH-stat group (p = NS*). As discussed in detail in part I of this study, 1 death occurred in the pulsatile group and 8 in the nonpulsatile group ($p = 0.018$).[19] Four patients in each of the alpha-stat and pH-stat groups had a neuroradiologically confirmed cerebrovascular accident (CVA) (p = NS among all groups), 5 of whom had multiple areas of cortical infarction consistent with cerebral emboli and 3 of whom subsequently died in the hospital. There was 1 in-hospital death from myocardial infarction in the noncardiac surgical cohort.

Table V presents summary statistics for patients in the CAB and noncardiac surgical groups on measures of neurologic and cognitive functioning at baseline and 7 days and 2 months after the operation. Classification of patients as exhibiting neurologic or cognitive impairment resulted in an incidence of neurologic dysfunction that ranged from 28% to 33% and cognitive dysfunction that ranged from 78% to 80% at 7 days across the four CAB treatment groups (p = NS; see Table VI). The incidence of any dysfunction (either neurologic or cognitive impairment) ranged from 82% to 87% (p = NS). At 2 months' assessment, the incidence of neurologic impairment had decreased to 17% to 18% and the incidence of cognitive impairment had decreased to 30% to 36% across the four groups. Of the 316 patients enrolled at the time of the 7-day assessment, 26 refused or were unavailable for either cognitive or neurologic testing, 15 patients underwent neurologic but not cognitive testing, a further 2 patients had incomplete cognitive testing, and 1 underwent cognitive but not neurologic assessment. At the 2-month follow-up assessment, 39 patients were unavailable for any testing, and 1 underwent cognitive but not neurologic assessment. A further 4 patients did not undergo any cognitive assessment, 26 were excluded from analysis of cognitive performance because of the lack of a 7-day cognitive assessment, and 8 were excluded from analysis for cognitive assessment because of incomplete cognitive testing at follow-up. Surviving patients who did not complete 7-day or 2-month assessments were similarly distributed among all four treatment groups for all circumstances associated with unavailability or exclusion (NS according to χ^2 test).

Neurologic and cognitive dysfunction by CAB treatment group. For the four CAB treatment groups (e.g., alpha-stat/pulsatile, alpha-stat/nonpulsatile, pH-stat/pulsatile, pH-stat/nonpulsatile), no interactions were found between pH management strategy, perfusion technique, and dysfunction (neurologic, cognitive, and either neurologic or cognitive, at 7 days and at follow-up). When analyzed according to either pulsatility or pH management, there were no significant differences between pH management strategy and perfusion technique.

*NS = Not significant.

Table III. *CAB and noncardiac surgical cohort demographics*

	Alpha-stat		*pH-stat*			
	Pulsatile (n = 79)	*Nonpulsatile (n = 79)*	*Pulsatile (n = 79)*	*Nonpulsatile (n = 79)*	*CAB total (n = 316)*	*Surgical cohort (n = 40)*
Age (yr)	60.9 ± 8.7	61.2 ± 7.8	60.2 ± 8.5	61.4 ± 8.4	60.9 ± 8.3	63.1 ± 8.4
Gender: M/F	66/13	65/14	70/9	63/16	264/52	28/12*
Educ (yr)	10.8 ± 2.9	11.2 ± 3.9	11.2 ± 3.4	11.0 ± 3.2	11.1 ± 3.4	11. ± 4.2
CVA/TIA	8	11	9	4	32 (10%)	3 (8%)
DM	20	17	8	13	58 (18%)	5 (13%)
MI <1/12	9	9	9	6	33 (10%)	0
LVEF <50%	23	23	29	22	97 (31%)	n/a
LVEF <35%	5	6	4	2	17 (5%)	n/a
Prev CAB	4	9	8	7	28 (9%)	4 (10%)

CAB, Coronary artery bypass study group; *Cohort,* noncardiac surgical control group; *Educ (yr),* years of education; *CVA/TIA,* history of cerebrovascular accident or transient ischemic attack; *DM,* diabetes mellitus; *MI* <1/12, myocardial infarction in previous month; *LVEF <35%,* patients with ventricular ejection fraction less than 35%; *Prev CAB,* previous coronary bypass surgery.

*p = 0.036 versus CAB group.

Table IV. *Operative characteristics of CAB group*

	Alpha-stat		*pH-stat*		
	Pulsatile (n = 79)	*Nonpulsatile (n = 79)*	*Pulsatile (n = 79)*	*Nonpulsatile (n = 79)*	*CAB total (n = 316)*
CAB >=4	10	16	22	17	65 (21%)
AoXC (min)	43.9 ± 17	44.1 ± 18	47.8 ± 17	46.9 ± 16	45.7 ± 17
CPB (min)	92.1 ± 29	95.1 ± 29	98.5 ± 37	98.6 ± 33	96.1 ± 32
CPB > 90 (*n*)	41	46	42	45	174
OR (min)	271 ± 48	280 ± 76	279 ± 59	282 ± 57	278 ± 61
PP (mm Hg)	17.1 ± 6.0*	1.8 ± 2.4	15.9 ± 6.6*	1.5 ± 2.2	NA
MABP (mm Hg)	57.9 ± 12	61.0 ± 11	57.2 ± 10	57.6 ± 12	58.4 ± 12
pHa†	7.42 ± 0.18§	7.43 ± 0.12§	7.26 ± 0.13	7.26 ± 0.06	NA
pHa‡	7.43 ± 0.06	7.43 ± 0.06	7.43 ± 0.05	7.43 ± 0.05	7.43 ± 0.05
$Paco_2$ (mm Hg)†	38.1 ± 4.1§	37.5 ± 4.1§	57.5 ± 6.9	59.3 ± 6.4	NA
$Paco_2$ (mm Hg)‡	37.2 ± 4.3	36.8 ± 4.9	38.5 ± 4.5	40.6 ± 6.5	38.3 ± 5.3
NPT (° C)	28.5 ± 2.1	28.5 ± 1.2	28.5 ± 2.0	28.2 ± 1.2	28.4 ± 1.7
Hgb (gm/L)	78.4 ± 18	78.9 ± 12	81.5 ± 15	78.4 ± 12	79.3 ± 14
Glu (mmol/dl)	10.6 ± 3.5	11.3 ± 3.0	10.4 ± 3.1	10.4 ± 3.0	10.7 ± 3.1
Hosp (days)	13.4 ± 11	12.2 ± 5	14.8 ± 25	12.9 ± 11	13.3 ± 15

CAB >=4, Patients receiving four or more coronary bypass grafts; *AoXC,* aortic crossclamp time; *CPB,* duration of cardiopulmonary bypass; *CPB > 90,* number of patients undergoing prolonged CPB; *OR,* duration of surgery; *PP,* pulse pressure; *MABP,* mean arterial blood pressure; *NPT,* mean nasopharyngeal temperature during hypothermic CPB; *Hgb,* lowest mean hemoglobin concentration during hypothermic CPB; *Glu,* highest mean glucose values during hypothermic CPB; *Hosp,* surgery to discharge time with in-hospital deaths excluded; *NA,* Not available.

*p < 0.001 versus nonpulsatile.

†Mean of all values measured at 37° C during hypothermic CPB.

‡Mean of all values measured at 37° C during normothermic CPB.

§p < 0.001 versus pH-stat.

These four groups were therefore collapsed and analyzed according to either pulsatility or pH management. Overall, there were no significant differences in the incidences of either neurologic or cognitive dysfunction at 7 days or 2 months between patients in the pulsatile or the nonpulsatile groups or between alpha-stat and pH-stat groups (Table VI).

Duration of CPB had been identified at the inception of the study as one of the uncontrolled variables of interest. Moreover, past research has identified duration of CPB as a risk factor for negative CNS outcome.[3-5] In our study, longer duration of CPB was found to be associated with increased CNS dysfunction. Post-hoc analysis was therefore undertaken to examine whether potential cerebroprotective effects of a given perfusion technique or pH management strategy would be most pronounced in those individuals undergoing CPB for a longer duration. Because mean duration of

Table V. *Neurologic and cognitive scores* by treatment group (mean ± standard deviation)*

	Baseline				
	Neurologic scale†	*Concentration‡*	*Grooved Pegboard time (sec)*	*Digit Symbol raw score*	*Associate Learning raw score§*
Entire CAB group	−1.4 ± 1.4	0.00 ± 0.86	89.4 ± 21.0	37.7 ± 10.0	22.7 ± 6.5
Alpha-stat group	−1.4 ± 1.5	−0.07 ± 0.89	89.7 ± 21.0	37.6 ± 10.0	23.0 ± 6.6
pH-stat group	−1.3 ± 1.4	0.07 ± 0.82	89.1 ± 21.0	37.8 ± 10.1	22.4 ± 6.3
Pulsatile group	−1.2 ± 1.3	0.01 ± 0.88	89.4 ± 20.6	37.9 ± 10.3	22.9 ± 6.5
Nonpulsatile group	−1.6 ± 1.5	−0.01 ± 0.84	89.5 ± 21.4	37.4 ± 9.7	22.5 ± 6.4
Alpha-stat/pulsatile group	−1.2 ± 1.2	−0.10 ± 0.88	90.5 ± 21.6	37.7 ± 10.4	23.6 ± 6.9
Alpha-stat/nonpulsatile group	−1.7 ± 1.6	−0.04 ± 0.91	88.9 ± 20.5	37.5 ± 9.5	22.4 ± 6.2
pH-stat/pulsatile group	−1.3 ± 1.4	0.11 ± 0.87	88.2 ± 19.7	38.2 ± 10.2	22.3 ± 6.0
pH-stat/nonpulsatile group	−1.4 ± 1.4	0.03 ± 0.76	90.0 ± 22.4	37.4 ± 10.0	22.5 ± 6.7
Noncardiac surgical control group	−1.7 ± 1.5	0.00 ± 0.88	89.4 ± 22.2	34.4 ± 9.7	23.3 ± 5.7

*For Grooved Pegboard time, higher scores reflect poor performance. For other measures, lower scores reflect poorer performance.
†Deficit from maximum attainable.
‡Concentration score = (Mental Control Z-score + Digit Span Z-score)/2.
§Associate Learning raw score = No. easy correct + 2(No. hard correct).
‖Deficit from baseline.

CPB was approximately 90 minutes, patients were arbitrarily grouped on the basis of CPB duration of less than or greater than 90 minutes, and neurologic and cognitive outcomes were analyzed according to CPB duration. The number of patients included in the long CPB duration group (CPB > 90 minutes) did not differ across treatment groups (41 alpha/pulse; 46 alpha/nonpulse; 42 pH/pulse; 45 pH/nonpulse; NS according to χ^2 test). Results of this post-hoc analysis revealed that for patients undergoing CPB of 90 minutes' duration or longer, the incidence of cognitive dysfunction was significantly ($p = 0.047$) lower at 2 months (Table VII, Fig. 1) in the alpha-stat group than in the pH-stat group.

Risk factors for dysfunction. Clinically relevant preoperative and intraoperative risk factors including age, weight, gender, presence of hypertension or insulin-dependent diabetes mellitus, previous CVA or transient ischemic attack, carotid stenosis (luminal narrowing >50%), duration of CPB, highest plasma glucose concentration during hypothermic or normothermic CPB, weight, and presence of preoperative neuropathy were examined univariately to determine significance of association with postoperative cognitive and neurologic dysfunction. Both neurologic and cognitive dysfunction at 7 days were found to be associated with CPB duration and age. At 2 months, neurologic dysfunction was related to history of hypertension, insulin-dependent diabetes mellitus, age, history of CVA or transient ischemic attack, normothermic glucose concentration, and carotid stenosis.

Factors identified by univariate analysis as significant, or as trending toward significance, were examined multivariately in a stepwise fashion. For either cognitive or neurologic dysfunction, significant correlations with increased age ($p = 0.0010$), longer duration of CPB ($p = 0.0053$), increased weight ($p = 0.0065$), and more years of education ($p = 0.0017$) were found at 7 days. At 2 months' follow-up, increased age ($p = 0.0007$) and presence of insulin-dependent diabetes mellitus ($p = 0.0242$) showed significant correlations with CNS dysfunction.

Neurologic and cognitive dysfunction in CAB versus noncardiac surgical cohort. Seventy-three percent (29/40) of patients in the noncardiac surgical cohort and 67% (211/316) of patients in the CAB group (p = NS) demonstrated preoperative neurologic abnormalities. In a younger group of 312 patients undergoing CAB, Shaw and associates[3] detected preoperative neurologic abnormalities in over 35%, whereas Carella and colleagues[7] found preoperative neurologic signs in 57.5% of patients in the CAB group. At 7-day assessment the trend was toward a higher incidence of neurologic dysfunction ($p = 0.085$) and a significantly higher incidence of cognitive dysfunction ($p = 0.003$) and of either cognitive or neurologic dysfunction ($p = 0.0002$) in the CAB group compared with the noncardiac surgical cohort. At 2 months the incidence of neurologic dysfunction was higher in the CAB group ($p = 0.050$), although the incidence of cognitive dysfunction did not differ between groups. Overall results are shown in Table VIII and Fig. 2.

Seven day				
Neurologic scale‖	*Concentration*‡	*Grooved Pegboard time (sec)*	*Digit Symbol raw score*	*Associate Learning raw score*§
−2.7 ± 2.8	−0.17 ± 0.91	102 ± 31.7	34.7 ± 11.0	20.5 ± 6.6
−3.0 ± 3.3	−0.21 ± 0.95	101 ± 31.9	35.1 ± 11.0	20.7 ± 7.5
−2.4 ± 2.2	−0.13 ± 0.87	103 ± 31.6	34.3 ± 11.0	20.2 ± 5.7
−2.5 ± 3.2	−0.21 ± 0.94	103 ± 35.1	34.8 ± 11.3	20.3 ± 6.5
−2.8 ± 2.5	−0.13 ± 0.88	100 ± 27.7	34.7 ± 10.6	20.6 ± 6.8
−2.7 ± 3.9	−0.28 ± 0.97	104 ± 36.6	35.0 ± 11.5	20.5 ± 7.1
−3.2 ± 2.6	−0.14 ± 0.93	98.3 ± 25.5	35.2 ± 10.4	21.0 ± 7.9
−2.3 ± 2.2	−0.13 ± 0.91	103 ± 33.7	34.6 ± 11.2	20.0 ± 6.0
−2.5 ± 2.2	−1.30 ± 0.84	102 ± 29.7	34.1 ± 10.9	20.3 ± 5.5
−2.2 ± 1.6	0.06 ± 0.82	93.0 ± 23.8	34.9 ± 14.3	22.6 ± 7.7

Discussion

Although the etiology of postoperative CNS dysfunction is likely multifactorial, microgaseous and particulate emboli are particularly culpable.[22-24] Equipment modifications such as arterial line filtration and use of membrane versus bubble oxygenators can decrease embolic load,[22, 23] although emboli are not entirely eliminated. Duration of CPB, as shown here and previously,[3-5] is an independent risk factor for postoperative neurologic and cognitive dysfunction. Therefore, the positive impact of protective strategies would likely be most apparent in patients undergoing CPB of prolonged duration, who are exposed to a greater embolic load. Post-hoc subanalysis of the CAB study groups, as a function of duration of CPB with prolonged CPB defined as 90 minutes or greater, demonstrated a lower incidence of cognitive dysfunction at 2 months for the group managed with alpha-stat pH management.

pH management strategies. Alpha-stat management has been shown to preserve cerebral flow/metabolism coupling such that hypothermia-induced decreases in metabolic rate are accompanied by proportionate decreases in cerebral blood flow.[4, 10, 17] In contrast, the increased carbon dioxide associated with pH-stat management induces cerebral vasodilatation and hyperemia resulting from pressure-passive changes in cerebral blood flow.[10-12, 17] The decreased incidence of cognitive dysfunction demonstrated 2 months after the operation in the alpha-stat group undergoing prolonged CPB is consistent with the hypothesis that fewer emboli are delivered into the cerebral circulation because of the proportionate decrease in cerebral blood flow relative to that of the pH-stat group.

In one of the few randomized studies of the influence of pH management strategy on postoperative neuropsychologic functioning reported to date, 86 patients with cardiac disease were assessed, and no difference in incidence of postoperative cognitive dysfunction between alpha-stat and pH-stat management was demonstrated.[15] In that study, however, no stratification for duration of CPB was made when results were analyzed, patients undergoing both open and closed chamber procedures were included, unfiltered bubble oxygenators were used, and pH-stat may not have been achieved in the treatment group.[25] Lack of a clear outcome benefit in those circumstances may reflect the effect of exposure to much greater numbers of emboli in comparison with patients in whom a filtered CPB circuit is used.[26] In addition, minimal differences in cerebral blood flow (and thus delivery of emboli into cerebral circulation) may have been present between their groups because of the small difference in actual arterial carbon dioxide tension (less than half that predicted).[25, 27] In contrast, a study of 65 patients by Stephan and coworkers[17] demonstrated improved neurologic outcome with alpha-stat pH management. They used membrane oxygenators and arterial line filtration in patients undergoing CAB operations and performed a neurologic examination before the operation and 7 days after the operation. Although cognitive testing was not performed on these patients, a higher incidence of neurologic dysfunction was found in patients in whom the pH-stat strategy (10/35) had been used than was found in those managed by the alpha-stat strategy (2/30). The 7% incidence of neurologic impairment reported in their alpha-stat group is lower than that which we observed (33%), however, and may reflect both differences in neurologic examination technique and their use of a younger study population (mean age 56 years, eldest aged 68

Table V. *Continued*

	Follow-up				
	Neurologic scale‖	*Concentration‡*	*Grooved Pegboard time (sec)*	*Digit Symbol raw score*	*Associate Learning raw score§*
Entire CAB group	−2.0 ± 2.2	0.12 ± 0.86	83.5 ± 20.7	41.2 ± 12.1	24.1 ± 7.0
Alpha-stat group	−2.1 ± 2.2	0.13 ± 0.85	82.3 ± 19.0	41.1 ± 11.1	24.0 ± 7.3
pH-stat group	−1.8 ± 2.2	0.11 ± 0.88	84.8 ± 22.3	41.2 ± 13.1	24.2 ± 6.8
Pulsatile group	−1.9 ± 2.1	0.09 ± 0.89	85.0 ± 23.8	41.0 ± 13.1	24.4 ± 7.2
Nonpulsatile group	−2.1 ± 2.3	0.16 ± 0.83	82.0 ± 17.0	41.3 ± 11.2	23.8 ± 6.9
Alpha-stat/pulsatile group	−1.9 ± 2.2	0.05 ± 0.82	81.9 ± 19.3	41.0 ± 12.1	24.4 ± 7.8
Alpha-stat/nonpulsatile group	−2.3 ± 2.3	0.23 ± 0.87	82.7 ± 18.9	41.2 ± 9.9	23.7 ± 6.6
pH-stat/pulsatile group	−1.8 ± 2.0	0.13 ± 0.97	88.6 ± 27.8	41.1 ± 14.1	24.5 ± 6.4
pH-stat/nonpulsatile group	−1.9 ± 2.3	0.10 ± 0.79	81.4 ± 15.3	41.3 ± 12.3	24.0 ± 7.2
Noncardiac surgical control group	−1.8 ± 1.7	0.23 ± 0.84	82.7 ± 24.2	36.9 ± 10.8	25.5 ± 7.0

*For Grooved Pegboard time, higher scores reflect poor performance. For other measures, lower scores reflect poorer performance.
‡Concentration score = (Mental Control Z-score + Digit Span Z-score)/2.
§Associate Learning raw score = No. easy correct + 2(No. hard correct).
‖Deficit from baseline.

Table VI. *Dysfunction by pH management and perfusion group*

	Alpha-stat	*pH-stat*	*Pulsatile*	*Nonpulsatile*
		Seven-day assessment		
Neuro	48/146 (33%)	40/143 (28%)	43/147 (29%)	45/142 (32%)
Cognitive	106/136 (78%)	109/137 (80%)	111/140 (79%)	104/133 (78%)
Either	117/142 (82%)	121/139 (87%)	119/142 (84%)	119/139 (86%)
		Two-month assessment		
Neuro	24/137 (18%)	23/139 (17%)	24/141 (17%)	23/135 (17%)
Cognitive	36/119 (30%)	43/120 (36%)	38/120 (32%)	41/119 (34%)
Either	53/125 (42%)	59/124 (48%)	56/126 (44%)	56/123 (46%)

p = Not significant for all between-group comparisons. *Neuro,* Neurologic dysfunction; *Either,* dysfunction on either cognitive or neurologic assessment.

Table VII. *Dysfunction by pH management group and CPB duration*

	Alpha-stat		*pH-stat*	
	7 days	*2 mo*	*7 days*	*2 mo*
		CPB < 90 min		
Neuro	16/68 (24%)	9/62 (15%)	13/68 (19%)	11/60 (18%)
Cognitive	48/66 (73%)	19/57 (33%)	48/66 (73%)	15/67 (26%)
Either	51/66 (77%)	25/59 (42%)	52/66 (79%)	21/59 (36%)
		CPB ≥ 90 min		
Neuro	32/78 (41%)	15/75 (20%)	27/75 (36%)	12/79 (15%)
Cognitive	58/70 (83%)	17/62 (27%)	61/71 (86%)	28/63 (44%)*
Either	66/76 (87%)	28/66 (42%)	69/73 (95%)	38/65 (58%)†

Neuro, Neurologic dysfunction; *Either,* dysfunction on either cognitive or neurologic assessment.
*p = 0.047 versus alpha-stat.
†p = 0.066 versus alpha-stat.

years). As demonstrated here and in other series, neurologic complications rise disproportionately with increased age.[1, 2] Finally, Patel and colleagues[18] used a standardized battery of 10 neuropsychologic tests before the operation and 6 weeks after the operation in a series of 70 patients undergoing CAB and randomized to alpha-stat or pH-stat strategies during nonpulsatile hypothermic CPB. They also demonstrated a significantly lower incidence of cognitive impairment 6 weeks after the operation (20% versus 48.6%, respectively) in the patients in whom alpha-stat management was used, incidences similar to our results.

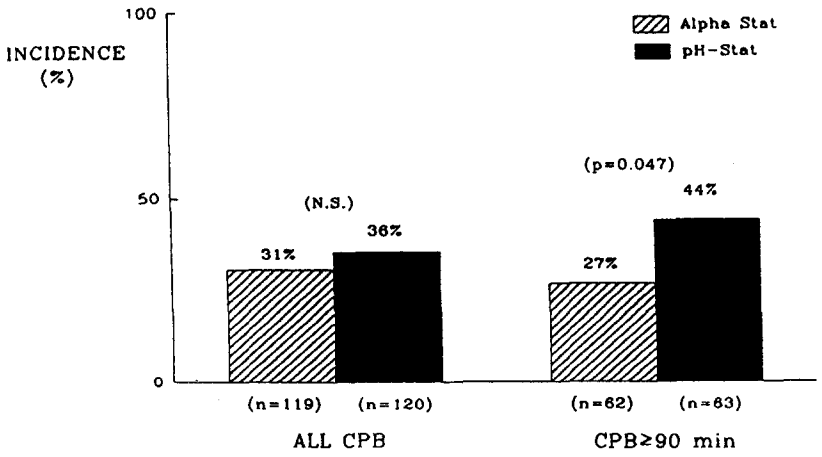

Fig. 1. Incidence of cognitive dysfunction 2 months after the operation for all patients in the CAB group and for those in whom CPB duration was 90 minutes or greater, excluding those in whom 7-day assessment was not available.

Table VIII. *Neurologic and cognitive dysfunction: CAB versus noncardiac surgical cohort*

	CAB group		*Surgical cohort*	
	7 days	*2 mo*	*7 days*	*2 mo*
Neuro	88/289 (30%)*	47/276 (17%)†	6/36 (17%)	1/30 (3%)
Cognitive	215/273 (79%)‡	79/239 (33%)	19/34 (56%)	10/25 (40%)
Either	238/281 (85%)§	112/249 (45%)	20/34 (59%)	11/26 (42%)

CAB group, Study group; *Surgical cohort,* noncardiac surgical control group. *Neuro,* neurologic dysfunction; *Either,* dysfunction on either cognitive or neurologic assessment.

*p = 0.085 versus surgical cohort.

†p = 0.050 versus reference cohort.

‡p = 0.003 versus surgical cohort.

§p = 0.0002 versus surgical cohort.

Perfusion techniques. Although by no means universal, nonpulsatile perfusion has remained the most common mode of perfusion during CPB. Increases in cerebral blood flow and improved cerebral perfusion in the presence of cerebral ischemia[13, 28] were factors leading to our decision to test the CNS effects of pulsatile perfusion in the current study. No significant differences in neurologic or cognitive outcome were apparent with the use of pulsatile perfusion in this study, however, similar to what has been reported by Henze, Stephan, and Sonntag.[16] This may reflect either that pulsatility is not important in influencing CNS outcome after CPB or that the characteristics of the pulsatile perfusion generated during CPB are insufficient to significantly influence postoperative brain function. We did, however, observe a significantly lower mortality rate and lower incidences of cardiovascular complications in the pulsatile perfusion group (see part 1 of this study),[19] similar to the results reported by Taylor and associates.[29]

Noncardiac surgical cohort. Although interest in neurologic dysfunction after CAB operations has been increasing, relatively few studies have incorporated a noncardiac surgical cohort to help isolate risk factors associated with CPB, independent from that of undergoing a major surgical procedure. Shaw and colleagues[3] demonstrated an increased incidence and severity of postoperative cognitive dysfunction in patients having CAB compared with a reference cohort of 50 patients undergoing peripheral vascular surgery (79% versus 31%) when assessed before hospital discharge, similar to our findings. The results of Smith[4] are also con-

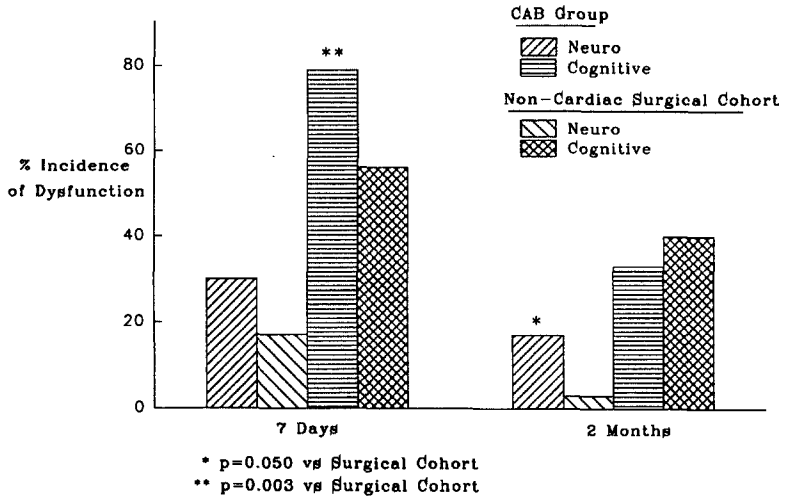

Fig. 2. Percentage incidence of neurologic and cognitive dysfunction in CAB group and noncardiac surgical cohort 7 days and 2 months after the operation.

sistent with our results in that at 8 days after the operation the incidence of moderate or severe cognitive deficit was significantly higher in a group of 67 patients having CAB, 73% versus 50%, respectively, than in a reference cohort of 24 patients having major vascular and non-CPB thoracic surgery. At 8 weeks after the operation, however, the incidences of neuropsychologic dysfunction were similar between groups at 37% and 44%, respectively. It was believed that different causes were involved in the genesis of impairment between the two groups, because patients in the reference cohort were older, had more extensive metabolic derangements (e.g., renal failure), and required more extensive pharmacologic support. Similarly, Hammeke and Hastings[8] reported that at 6 months postoperatively, the incidence of cognitive dysfunction was comparable in both a group of 24 patients having CAB and a group of eight patients having peripheral vascular surgery; this study was criticized, however, because some of the tests used were not suitable for repeat assessments and because of the small number of patients available at follow-up.[30] We also found a significantly higher incidence of cognitive dysfunction at 7 days and no difference in incidence of cognitive dysfunction at 2 months, but we did demonstrate a significantly higher incidence of postoperative neurologic dysfunction at 2 months (17% versus 3%), in comparison with a noncardiac surgical cohort. Notably, none of the aforementioned studies assessed postoperative neurologic function.

The current results suggest that CAB operations are associated with a significantly greater incidence of cognitive dysfunction in the early postoperative period and a greater incidence of neurologic dysfunction at follow-up than are operations in which CPB is not used. The high incidence of preoperative neurologic abnormalities detected in both the CAB and the surgical cohort, and the similar incidences of cognitive dysfunction in both groups at 2 months after the operation, also suggests that these patients may have a particular susceptibility to CNS dysfunction because of associated disease processes (e.g., incipient cerebrovascular atherosclerosis). This susceptibility may render them at greater risk from all procedures involved with major surgery (e.g., sedation/analgesics, intensive care management) rather than cardiac surgery exclusively.

As proposed by Strittmatter and associates,[31] patients with apolipoprotein E-ϵ4 genotypes demonstrate impaired neuronal reparative processes and are at increased risk of earlier onset of Alzheimer disease. These genotypes also appear to be at slightly increased risk of atherosclerosis and coronary artery disease[32] and thus may form a group that may be more susceptible to CNS injury. This is consistent with preliminary data from Tardiff and coworkers,[33] which demonstrated a correlation between apolipoprotein E-ϵ4 profile and cognitive dysfunction in patients undergoing CPB.

Additionally, cognitive dysfunction at 2 months is less prevalent after 90 minutes of CPB in patients

managed with alpha-stat than with pH-stat strategy. This finding was obtained on a post-hoc analysis and, although consistent with findings of some prior research,[17, 18] it is subject to replication in future prospective studies. Finally, our results suggest that both neurologic and cognitive measures contribute uniquely to estimates of post-CPB morbidity. Thus concomitant assessment of both parameters is necessary to more fully quantify postoperative CNS dysfunction.

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Appendix I (Western Perioperative Neurologic Scale—Guide)

This scale is designed to detect and quantify anatomically discrete neurologic abnormalities. It is not intended as an assessment of neurologic functioning. Test/re-test reliability of the neurologic examination was demonstrated by having the same examiner administering the same structured neurologic examination over a 7-day interval to a group of 28 patients convalescing in the hospital for more than 1 month after CVA (intraclass correlation coefficient = 0.986).

Mentation

Level of consciousness: Assessment of patient orientation, concentration, memory, and mental functioning. Orientation is based on the patient's awareness of time, place, and person where *person* refers to the patient as able to give name and address, *place* to identify the city and or name of the hospital, and *time* where the patient must give at least the correct month and year. If early in the month (i.e., first 3 days) previous month is acceptable. Speech may be dysarthric (mispronounced or slurred) but intelligible. If for any reason the patient cannot answer specific questions on orientation (i.e., does not know the answer, gives the wrong answer, answers only partially, cannot express himself or herself either by lack of words or unintelligible speech or finally ignores questions), he or she is are considered disoriented.

3. Normal: Normal consciousness, fully conscious. The patient is alert, attentive, aware, and appropriate.
2. Drowsy: The patient when stimulated remains awake and alert for a short time but tends to doze off even during the examination. Lethargic but mentally intact.
1. Stuporous: The patient is obtunded, responds to loud verbal stimuli and/or strong touch; may vocalize but does not become alert or completely awake.
0. Comatose: The patient responds to deep pain such as sternal pressure, but (1) only by purposeful movement of a limb toward noxious stimuli and/or grimacing and/or moaning (no verbal response); (2) by nonpurposeful movements, flexion of upper limbs (decortication), or extension of upper limbs (i.e., decerebration); (3) no response to noxious stimuli.

Speech. For the assessment of language/speech, either motor ability such as speaking or writing or sensory ability such as auditory or visual or mixed will be considered. Test for comprehension and response either verbally or nonverbally.

3. Normal: The patient answers all commands and questions, the conversation is fluent, and there is good comprehension of verbal language. If the patient is intubated, the patient can carry out a three-step command.
2. Dysphasia: The patient may have slurred speech (dysarthria) but is still intelligible, is able to follow complex commands but may show hesitancy, may misspell words or make mistakes when reading aloud. The intubated patient can follow a two-step command or can be understood through writing or "reading lips."
1. Aphasia: Expressive aphasia (Broca's) or receptive asphasia (Wernicke's). *Broca's:* Speech is halting or laborious, omitting connectives, able to comprehend and identify objects by name. *Wernicke's:* Speech is easy and fluent but with little or no meaning. Inappropriate words are juxtaposed with no insight and jargon is common. May neither understand nor follow commands or may be mute but comprehends. The patient is able to carry out a single-step command.
0. Mute: Global aphasia. The patient is unable to comprehend or follow command.

Patients should always be scored according to their worst speech deficit (i.e., language score or mispronunciation).

Memory. Testing to include short term and long term, may include digit span, recall, and the spelling of words backward.

3. Normal: The patient is able to recall three words of three at 5 minutes.
2. Mild deficit: The patient is able to recall two of the three words within 5 minutes or three of three with prompting.
1. Moderate deficit: The patient is able to recall one word of three at 5 minutes or two of three with prompting.

0. Severe deficit: The patient is unable to recall any words of the three given even with prompting.

Cranial nerves

Vision. Assessment of visual acuity, visual fields, conjugate and convergence of pupils, ocular movements, and pupillary reaction.

3. Normal: No visual loss, normal acuity with correction, normal visual fields (no change from the baseline). Normal extraocular movements, response to threat.
2. Mild deficit: Inattention, partial palsy, partial field cut, a new diplopia, a change in extraocular movements. One modality not elicited (i.e., abnormal extraocular movement).
1. Moderate deficit: Dense hemianopsia and pupillary deviation, monocular hemianopsia. Two modalities absent.
0. Severe deficit: Functionally blind (i.e., the patient is able to see only large moving objects such as a hand); the patient does not respond to testing. All modalities abnormal or absent.

Cranial nerves. To assess the cranial nerves for facial motor function—V, VII, XII—as it pertains to the face, tongue movement, and airway protection.

3. Normal: No weakness, facial symmetry. Normal gag reflex, tongue, and facial movement.
2. Mild deficit: One of the areas show weakness, that is, facial asymmetry, poor airway protection.
1. Moderate deficit: Two of the areas tested show weakness, that is, unilateral facial paralysis.
0. Severe deficit: All of the areas tested show weakness, that is, dense facial palsy, loss of gag reflex, and unable to protect the airway.

Motor. Testing of motor strength, both the upper and lower limbs, right and left sides. When strength or range of movement is being tested, the same resistance and position of pressure application must be submitted to each limb. Motor function can be monitored by the ability of the patient to maintain a fixed posture in the upper or lower limb for 3 to 5 seconds; the observer will alternately place the limb in the desired position.

UPPER LIMBS. Place the arms outstretched at 90 degrees in front of the patient. *Equal motor response:* The patient can maintain the fixed posture equally in both upper limbs for a few seconds or withdraws equally on both sides to pain. *Unequal motor response:* The patient cannot maintain equally on both sides the fixed posture, weakness is noted on one side, or there is an unequal withdrawal to pain. Note side where the withdrawal is not as brisk.

LOWER LIMBS. Flexion to thighs with knees flexed at 90 degrees. *Equal motor response:* The patient can maintain the fixed posture equally in both lower limbs for a few seconds or withdraws equally on both sides to pain. *Unequal motor response:* The patient cannot maintain the fixed posture equally on both sides, weakness is noted on one side, or there is an unequal withdraw to pain. Note side where the withdrawal is not as brisk.

In the postoperative period, testing will be modified because of limitations of activity and accessory medical interventions such as intravenous lines and chest tubes. Test both upper and lower limbs, proximal and distal to flexion, extension and appropriate withdrawal. Test using either central stimuli (glabellar pressure) or peripheral stimuli (nailbed pressure) on the very drowsy patient.

UPPER LIMB PROXIMAL. The patient should be tested while in the sitting position if possible. To test, abduct the arms to 90 degrees. If the patient is lying in bed, elevate arms to approximately 45 to 90 degrees. Test strength in both arms simultaneously, resistance being applied to the midpoint between the shoulder and the elbow.

UPPER LIMB DISTAL. The patient is tested in either lying or sitting position with the arms elevated. To test, the patient is asked to make a fist and to extend the wrists. A comparison range of movement in both wrists is made simultaneously. If the patient has full range of motion in both wrists, test strength by applying resistance separately to both fists while stabilizing the arm firmly. Grip strength is also tested in both hands.

LOWER LIMBS. The patient should be lying in the bed for all testing and scored on the worst deficit of either hip flexion or dorsiflexion. *Hip flexion:* Ask the patient to flex thighs toward the trunk with the knees flexed at 90 degrees. Movement in both thighs is tested separately. *Dorsiflexion:* Have the patient point the toes and foot upward. Compare both feet simultaneously (i.e., complete or partial movement). In both cases apply resistance alternately to each thigh and foot after full movement has been completed to testing of strength. *Dorsal extension:* Have the patient extend the toes and foot downward and apply resistance.

3. Normal: No detectable weakness. The patient is able to flex or extend the limb, appropriate withdrawal or localization.
2. Mild weakness: Mild drift, apraxia, normal range of motion against gravity, but succumbs to resistance by observer either partially or totally. Also note the loss of rapid fine movements. Abnormal flexion of the extremity.
1. Moderate weakness: Gross drift. Cannot completely overcome gravity in the range of motion (i.e., partial movement). Abnormal extension of the extremity.
0. Severe weakness: Paresis of limb or neglect. Absence of motion in movement tested or only contraction of muscles without actual movement of the limb. No motor response or flaccid.

Sensation and cerebellum

Sensation. Testing of the right and left sides for light touch, temperature, vibration, and position sense. The right and the left sides should be assessed separately.

3. Normal: No sensory deficit to any of the modalities tested.
2. Mild deficit: Partial sensory or motor loss, tingling or numbness, inattention, loss of one modality.
1. Moderate deficit: Unable to complete modality, loss of sensation of more than one modality.
0. Severe deficit: Total sensory loss of all sensation, no response to painful stimuli.

Cerebellar. Testing includes finger-nose, heel-shin, and rapid tapping, nystagmus, ataxia, and incoordination. Posture should be observed when the patient is sitting or standing.

3. Normal: Intact
2. Mild deficit: Loss of finger-nose, or heel-shin, or tapping: mild ataxia, involving only one limb.
1. Moderate deficit: Loss of two of the modalities; gross ataxia.
0. Severe deficit: Severe impairment of cerebellar function to all modalities.

Reflexes. The reflexes to be tested include jaw jerk, biceps, triceps, brachioradialis, knee, ankle, and plantar on both the right and the left sides.

3. Normal: All reflexes are intact; toes downgoing.
2. Mild deficit: One reflex is noted to be different in either the upper or lower limb (i.e., hyperreflexive arm or leg).
1. Moderate deficit: Hyporeflexive or hyperreflexive side (i.e., arm and leg).
0. Severe deficit: All reflexes abnormal (i.e., hyperactive in both arms and legs and bilateral upgoing toes) and clonus.

Primitive reflexes. The primitive reflexes tested include grasp, palmomental, glabellar tap, sucking, and snout (pout).

3. Absent: No primitive reflexes observed.
2. One primitive reflex present.
1. Two primitive reflexes present.
0. All primitive reflexes present.

Gait. Testing to include stance, gait, and Romberg.

3. Normal: The gait is intact.
2. Mild deficit: Wide-based stance, unsteady on feet, slight hemiparesis.
1. Moderate deficit: Marked hemiparesis; the patient may be able to stand with assistance but would fall if not supported.
0. Severe deficit: Unable to stand.