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A Randomized Study of Carbon Dioxide Management during Hypothermic Cardiopulmonary Bypass

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Eighty-six patients undergoing coronary artery bypass graft (n = 63) or intracardiac (n = 23) surgery were randomly assigned with respect to the target value for Pa_{CO_2} during cardiopulmonary bypass. In 44 patients the target Pa_{CO_2} was 40 mmHg, measured at the standard electrode temperature of 37° C, while in 42 patients the target Pa_{CO_2} was 40 mmHg, corrected to the patient's rectal temperature (lowest value reached: mean 30.1, SD 1.9° C). Other salient features of bypass management include use of bubble oxygenators without arterial filtration, flows of 1.8–2.4 $l \cdot min^{-1} \cdot m^{-2}$, mean hematocrit of 23%, and mean arterial blood pressure of approximately 70 mmHg, achieved by infusion of phenylephrine or sodium nitroprusside. Neuropsychologic function was assessed with series of tests administered on the day prior to surgery, just before discharge from the hospital (mean 8.0, SD 5.8 days postoperatively, n = 82), and again 7 months later (mean 220.7, SD 54.4 days postoperatively, n = 75). The scores at 8 days showed wide variability and generalized impairment unrelated to the Pa_{CO_2} group or to hypotension during cardiopulmonary bypass. At 7 months no significant difference was observed in neuropsychologic performance between the Pa_{CO_2} groups. Regarding cardiac outcome, there were no significant differences between groups in the appearance of new Q-waves on the electrocardiogram, the postoperative creatine kinase-MB fraction, the need for inotropic or intraaortic balloon pump support, or the length of postoperative ventilation or intensive care unit stay. These findings support the hypothesis that CO_2 management during cardiopulmonary bypass at moderate hypothermia has no clinically significant effect on either neurobehavioral or cardiac outcome. (Key words: Acid–base balance. Cardiopulmonary bypass. Hypothermia. Outcome: neuropsychologic.)

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THE QUESTION of optimal blood gas management during deliberate hypothermia has been the subject of much debate.[1–6] Two approaches have been advocated. The first is to adjust the arterial partial pressure of CO_2 to maintain the blood near *p*H 7.40 at the patient's body temperature. The readings from the blood–gas analyzer must then be mathematically corrected because they are conventionally made at an electrode temperature of 37° C. This approach has come to be known as "*p*H-stat" management because it seeks to achieve a constant arterial *p*H as the patient's temperature varies.

The other approach, known as "α-stat" management, was suggested by Rahn *et al.*[7] as a means to preserve cellular metabolism during varying temperatures by keeping a constant state of electrochemical dissociation of the ionizable amino acids (principally the α-imidazole group of histidine); α-stat management requires that the total CO_2 content of the blood remain constant with cooling (in the absence of metabolic acidosis or alkalosis). Because this mirrors the situation in which a blood sample is warmed anaerobically for analysis in a blood–gas machine, α-stat can be approximated by adjusting the patient's arterial CO_2 tension to give blood–gas analyzer readings of 40 mmHg, without correction, regardless of body temperature. With this approach the increased solubility of CO_2 during hypothermia results in a decrease in P_{CO_2}, producing a respiratory alkalosis when blood–gas values are corrected for temperature.

Studies in dogs have found that alkalosis during hypothermia results in increased cardiac index,[8] increased cardiac oxygen utilization and lactate extraction,[8,9] increased myocardial contractility,[8] increased subendocardial blood flow,[8] and less tendency for ventricular fibrillation.[10] However, *p*H does not influence performance of the isolated rat heart during hypothermia.[11]

Theoretically, the enzymes of brain metabolism should function better under α-stat management.[12] However, many anesthesiologists practice *p*H-stat management because of concerns that hypocapnia will reduce cerebral oxygen delivery due to a leftward shift in the oxyhemoglobin dissociation curve and a reduction in cerebral blood flow.[2,3,5] Recent clinical studies simultaneously measuring global cerebral blood flow and metabolism during hypothermic bypass with α-stat management found luxury

cerebral perfusion, *i.e.*, the reduction in oxygen delivery with decreasing temperature was less than the reduction in the metabolic needs of the brain.[13,14] Moreover, cerebral autoregulation was lost during *p*H-stat management, allowing a further excess of cerebral blood flow over the metabolic requirements.[14] It has been suggested that unregulated cerebral blood flow could injure the brain by causing a "steal" phenomenon in patients with cerebrovascular disease or by increasing delivery to the brain of the shower of microemboli emanating from the bypass machine.[14–16]

To determine whether the known physiologic responses to CO_2 management during cardiopulmonary bypass (CPB) with moderate hypothermia affect the cerebral or cardiac outcome of patients, we designed a randomized clinical trial to compare the α-stat and *p*H-stat regimens. A secondary objective was to assess the influence of hypotension during CPB on postoperative brain function.

Materials and Methods

With institutional approval and informed consent, we studied 86 patients undergoing coronary artery bypass graft (CABG, n = 63) or intracardiac (n = 23) surgery. These patients are a subset, randomized with respect to CO_2 management, of the 90 patients reported in a study comparing neuropsychologic test results between cardiac surgery patients and nonsurgical controls.[17] Patients were recruited for the study without regard to the severity of their cardiac disease and without screening for neurologic disease, as long as they had adequate comprehension of the English language and were well enough to undergo the requisite neuropsychologic testing. Patients requiring urgent or emergent surgery were excluded as well as those who did not live within a reasonable distance to allow for follow-up evaluation.

The neuropsychologic tests were administered by trained psychometrists, blinded to the CO_2 group assigned, on the day preceding surgery (designated preoperative), just prior to discharge from the hospital (mean 8.0, SD 5.8 days postoperatively; designated postoperative) and again an average of 7 months later (mean 220.7, SD 54.4 days postoperatively; designated follow-up). The tests included the following: Shipley Institute of Living Scale; Logical Passages and Visual Designs from the Wechsler Memory Scale (WMS); Selective Reminding Test (SRT); Visual Search and Digit Vigilance tasks from the Repeatable Cognitive-Perceptual-Motor Battery; Digit Symbol subtest from the Wechsler Adult Intelligence Scale-Revised; and the Aphasia Screening Test, Trail Making Test, Sensory Perceptual Examination, and Finger Tapping Test from the Halstead Reitan Neuropsychological Test Battery. The testing required approximately 2 h to complete. Details concerning these tests and a review of the application of neuropsychologic testing in cardiac surgical patients have been presented elsewhere.[17,18]

Preanesthetic medication consisted of oral diazepam (0.15 mg/kg body weight) and intramuscular morphine sulfate (0.15 mg/kg). Anesthesia was induced with iv diazepam (0.1–0.2 mg/kg), fentanyl (50 μg/kg), and pancuronium bromide (0.15 mg/kg). Following tracheal intubation, anesthesia was maintained with a constant 0.5% concentration of enflurane, administered continuously into the breathing circuit or pump oxygenator. Hemodynamic changes were treated with vasopressors or vasodilators. Supplemental doses of opioid and diazepam were administered as needed after discontinuing CPB, and no attempt was made to standardize the administration of opioid or sedative agents in the postoperative period.

Prebypass, anticoagulation was achieved with 400 U/kg of intestinal mucosa heparin, supplemented as needed to maintain an activated clotting time of at least 480 s during CPB. Bubble oxygenators (Bentley Laboratories, Irvine, California) were used. The circuit was primed with lactated Ringer's solution, mannitol (1 g/kg), and blood, if necessary, to achieve a hematocrit of approximately 25% during bypass. The priming solution was circulated through a prebypass filter; no arterial line filtration was employed during bypass. Nonpulsatile perfusion was at index of 2.4 $l \cdot min^{-1} \cdot m^{-2}$ at normothermia, usually tapered to 1.8 $l \cdot min^{-1} \cdot m^{-2}$ at the minimum rectal temperature of 28–32° C. Mean arterial blood pressure was controlled with iv phenylephrine or sodium nitropusside, with a target range of 60–80 mmHg. Oxygen inflow to the oxygenator was 6 l/min, or higher if needed to achieve satisfactory arterial oxygenation.

A random number table was used to allocate patients

TABLE 1. Components of Summary Change Scores of Neuropsychologic Impairment

Visual motor	Ratings of drawings on Aphasia Screening Test
	Wechsler Memory Scale: Drawings
	Immediate memory
	Delayed recall
Verbal memory	Wechsler Memory Scale
	Trials to a criterion of 15 memories
	Number of memories at last trial
	Number of memories at delay
	Selective Reminding Test
	Number of trials to criterion
	Sum of words recalled
	Delayed recall
Aphasia	Verbal items of the Aphasia Screening Test
Complex problem solving	Trails B, time
	Shipley Abstract Reasoning, raw score
	Digit Symbol
Overall impairment	Sum of above summary scores

TABLE 2. Comparison of CO_2 Groups, Data from Bypass

	α-stat	pH-stat	P Value
Pa_{CO_2} (mmHg, Unc)	40.2 ± 1.3	47.3 ± 3.4	<0.001
Pa_{CO_2} (mmHg, Cor)	32.8 ± 1.3	38.1 ± 2.1	<0.001
pH_a, Unc	7.38 ± 0.03	7.32 ± 0.04	<0.001
pH_a, Cor	7.45 ± 0.03	7.39 ± 0.04	<0.001
CPB time (min)	89.9 ± 28.1	103.7 ± 57.4	0.16
AOT (min)	49.0 ± 17.0	58.5 ± 35.3	0.11
MRT (°C)	30.1 ± 2.0	30.1 ± 1.8	0.89
MHct (%)	22.8 ± 3.0	23.0 ± 2.8	0.71
MAP (mmHg)	71.1 ± 6.0	71.4 ± 7.7	0.83
MIN2 (mmHg)	42.3 ± 7.8	41.3 ± 9.6	0.61
MAX2 (mmHg)	96.1 ± 12.9	92.6 ± 11.7	0.24
TM50 (mmHg · min)	40.6 ± 55.7	34.8 ± 58.2	0.23
Lotime (min)	5.1 ± 4.6	8.2 ± 9.4	0.34
SNP (mg)	2.66 ± 3.67	2.72 ± 3.54	0.91
PHE (mg)	1.65 ± 1.58	2.01 ± 2.24	0.99

Values are expressed as mean ± SD.

CPB = cardiopulmonary bypass; AOT = aortic occlusion time; MRT = minimum rectal temperature; MHct = minimum hematocrit; MAP = mean arterial pressure over bypass run; MIN2 = lowest 2-min epoch of mean arterial pressure; MAX2 = highest 2-min epoch of mean arterial pressure; Lotime = time with arterial pressure <50 mmHg during bypass; Cor = corrected to rectal temperature; Unc = uncorrected; SNP = sodium nitroprusside; PHE = phenylephrine.

Unpaired *t* tests were used except Mann-Whitney tests for CPB time, AOT, Lotime, SNP, and PHE.

(by blocks in a balanced manner for each of four surgeons) to one of two groups: 1) maintenance of Pa_{CO_2} during CPB at 40 mmHg at the standard electrode temperature of 37° C (α-stat), or 2) maintenance at 40 mmHg corrected to rectal temperature (*p*H-stat). Blood–gas samples were analyzed every 10 min during bypass by one blood–gas analyzer (Instrumentation Laboratories Model 813), calibrated according to the manufacturer's recommendations and having quality control verified with tonometered blood.[19] Temperature correction (for the *p*H-stat group) was performed automatically by the blood–gas instrument. CO_2 inflow to the oxygenator was adjusted according to blood gas results to maintain the desired Pa_{CO_2}.

Mean arterial blood pressure (MAP) was recorded every 5 s during CPB, using a data acquisition system described previously.[20] Later a digital filtering scheme smoothed the data into 2-min epochs. A hypotension index, TM50, defined by Stockard *et al.*,[21] was then calculated as the area between the smoothed MAP-*versus*-time curve and the 50 mmHg line, when the MAP was less than 50 mmHg during bypass. The total time during bypass when the MAP was below 50 mmHg (designated Lotime) was also calculated. Patients were dichotomized depending on whether they experienced substantial hypotension or not by the criterion of Stockard *et al.*[21] (TM50 > 100 mmHg · min), and these groups were used to compare neuropsychologic outcomes.

Cardiac outcome was assessed by conventional clinical measures. Data recorded in the operating room were the number of defibrillations necessary to produce an organized cardiac rhythm following removal of the aortic occlusion clamp and the need for infusion of inotropic drugs and intraaortic balloon counterpulsation. Postoperatively, blood samples for creatine kinase (CK) were obtained upon arrival in the intensive care unit (ICU) and again at 12 and 24 h postoperatively. The CK-MB fraction was considered to be elevated if it exceeded 20 U/l on any sample. Twelve-lead electrocardiograms were obtained upon arrival in the ICU and at least daily while the patient remained in the ICU. All postoperative electrocardiograms of patients with elevated CK-MB were reviewed for the presence of new Q-waves. The time to extubation, use of inotropic support, and duration of ICU stay were also recorded.

The individual neuropsychologic tests were compared by CO_2 groups for the three testing sessions: preoperative, postoperative, and follow-up. In addition, we formulated five indices (called summary change scores) to summarize the changes in broad categories of neuropsychologic functioning from baseline (table 1). We grouped the scores of similar measures to amplify the observed effect of CPB upon these areas of functioning. To combine tests with disparate scoring scales, the individual scores on each test postoperatively and at follow-up were normalized by subtracting the mean and dividing by the standard deviation of the corresponding preoperative score of the combined patient and control groups from our previously reported study.[17] Next, scores that decline with increasing impairment (*e.g.*, the number of items completed in a timed task) were multiplied by −1 to give a consistent orientation, with higher scores always representing greater impairment. Finally, the components were added to give the

TABLE 3. Cardiac Outcome by CO_2 Groups, Continuous Variables

	α-stat	pH-stat	P Value
Defibrillations on CPB	2.2 ± 5.5 (44)	1.2 ± 1.4 (41)	0.27
Time to extubation (h)	20.2 ± 13.8 (44)	21.0 ± 12.0 (41)	0.76
Time in ICU (days)	2.3 ± 1.4 (44)	2.4 ± 1.3 (40)	0.91
CK, total (IU)	610.9 ± 475.1 (44)	540.1 ± 425.7 (41)	0.47
CK-MB fraction (IU)	16.4 ± 10.0 (44)	13.5 ± 6.4 (41)	0.12

Values are expressed as mean ± SD; N is given in parentheses.

TABLE 4. Cardiac Outcome by CO_2 Groups, Dichotomous Variables

	Number with Trait/ Sample N		
	α-stat	pH-stat	P Value
Inotropic support in OR	4/44	7/42	0.47
Balloon pump in OR	0/44	1/41	0.97
Elevated CK-MB fraction	10/44	6/41	0.50
New Q-waves on ECG*	2/10	1/7	1.00
Inotropic support in ICU	4/44	7/41	0.44

* Of those patients with elevated CK-MB.

summary measures, and change scores were then calculated as the difference in summary measures: postoperative minus preoperative or follow-up minus preoperative, respectively.

Comparisons of the CO_2 groups were made using the two-sample *t* test or the Mann-Whitney test (when there were major differences in the sample sizes). Reported *P* values have not been adjusted for multiple comparisons. Indices of myocardial injury and performance were compared by the Mann-Whitney test for continuous variables, and the chi-square test (with correction for continuity) or Fisher's exact test for the binary variables. Comparisons of the high and low TM50 groups were made with the Mann-Whitney test, and tests of association between TM50 and the neuropsychological change scores were done by Pearson's correlation coefficient. Statistical computations were performed using SPSS™ and SAS™. A two-tailed significance level of 0.05 was used throughout.

Results

Forty-four patients were randomized to α-stat management (mean age ± SD, 58.3 ± 11.0 yr) and 42 to *p*H-stat management (mean age ± SD, 60.1 ± 10.1 yr). There were no differences between groups approaching statistical significance with respect to sex, occupational group, education, height, weight, preoperative CK (total and MB fraction), or left ventricular ejection fraction. Four patients (all in the *p*H-stat group) had recovered from strokes in the remote past. Intraoperatively, the means of the corrected and uncorrected P_{CO_2} and *p*H values over the period of CPB were significantly different between groups, but no significant differences occurred in the other variables related to CPB (table 2).

TABLE 5. Neuropsychologic Scores at Preoperation

	α-stat			pH-stat				Confidence Limits*	
	Mean	SD	N	Mean	SD	N	P Value	Lower	Upper
Shipley									
Vocabulary IQ	118.8	15.3	39	119.9	17.1	38	0.78	−6.2	8.4
Abstract IQ	91.3	19.0	39	94.3	22.3	39	0.52	−6.3	12.3
Conceptual IQ	79.8	15.4	38	82.0	17.2	38	0.55	−5.3	9.7
Trails									
A time	34.4	11.3	44	34.7	14.3	42	0.90	−5.2	5.8
B time	95.0	38.4	44	95.7	42.0	42	0.94	−16.6	18.0
WMS									
Verbal immediate	15.5	2.8	43	15.1	3.1	41	0.60	−0.9	1.7
Verbal delay	12.4	4.2	42	12.4	3.7	40	0.98	−1.7	1.8
No. of trials	3.4	1.5	41	3.2	1.7	41	0.48	−0.9	0.5
Visual immediate	7.5	3.2	43	8.9	3.3	41	0.05	−0.02	2.8
Visual delay	6.0	3.2	42	6.6	3.7	40	0.42	−0.5	1.7
SRT									
Trials	9.9	2.1	43	9.5	2.2	41	0.43	−1.3	0.5
Memories, last trial	8.4	1.8	43	8.6	1.6	41	0.61	−0.5	1.1
Sum recall	70.9	18.5	43	74.6	14.1	41	0.30	−3.5	10.9
Delayed recall	5.6	2.9	43	6.2	2.7	41	0.30	−0.6	1.8
Visual search time	172.3	97.5	39	196.1	98.8	35	0.30	−21.7	69.3
Digit vigilance time	122.4	32.5	44	124.7	39.4	42	0.77	−13.2	17.8
Digit symbol	47.0	12.6	44	44.0	11.3	42	0.25	−8.2	2.2
Aphasia									
Verbal	7.2	4.2	44	8.5	6.1	41	0.24	−1.0	3.6
Drawings	4.1	2.0	44	3.6	1.8	41	0.27	−1.3	0.3
Finger agnosia									
Right	1.2	3.6	31	1.5	3.9	27	0.80	−1.7	2.3
Left	1.2	3.7	31	1.3	4.0	26	0.91	−1.9	2.1
Fingertip no. writing									
Right	2.7	3.9	30	3.3	4.2	26	0.60	−1.6	2.8
Left	2.4	3.7	30	2.7	4.5	25	0.76	−1.9	2.5
Tapping dominant	45.0	7.8	44	48.3	6.0	41	0.03	0.3	6.3

* Exact 95% confidence limits, α-stat minus *p*H-stat.

TABLE 6. Neuropsychologic Scores at Postoperation

	α-stat			pH-stat				Confidence Limits*	
	Mean	SD	N	Mean	SD	N	P Value	Lower	Upper
Trails									
A time	43.9	19.0	41	47.1	22.7	41	0.50	−3.9	10.3
B time	134.2	79.1	41	144.9	80.2	41	0.54	−24.3	45.7
WMS									
Verbal immediate	13.6	4.9	39	14.0	4.1	39	0.67	−2.8	2.5
Verbal delay	9.8	5.5	38	10.3	4.8	39	0.73	−5.8	4.4
No. of trials	3.9	1.9	39	3.3	1.8	39	0.14	−1.4	0.2
Visual immediate	6.5	3.5	40	6.8	3.7	40	0.71	−1.3	1.9
Visual delay	4.3	3.9	39	4.4	3.5	40	0.94	−1.6	1.8
SRT									
Trials	10.9	0.6	40	10.7	0.8	39	0.34	−0.5	0.1
Memories, last trial	6.5	2.8	40	6.3	2.3	39	0.68	−1.4	1.0
Sum recall	57.3	23.5	40	56.5	18.7	39	0.87	−10.3	8.7
Delayed recall	3.4	2.8	40	2.9	2.6	39	0.47	−1.7	0.7
Visual search time	331.4	208.1	33	377.1	205.9	35	0.36	−54.3	145.7
Digit vigilance time	162.5	61.3	41	173.9	63.4	41	0.41	−16.0	38.8
Digit symbol	38.9	18.9	40	33.4	14.2	40	0.15	−12.9	1.9
Aphasia									
Verbal	9.4	11.3	41	10.5	12.4	41	0.68	−4.1	6.3
Drawings	4.6	2.2	41	4.8	2.9	41	0.80	−0.9	1.3
Finger agnosia									
Right	7.9	9.2	31	8.8	9.4	33	0.70	−3.7	5.5
Left	7.9	9.2	31	9.2	9.3	32	0.57	−3.4	6.0
Fingertip no. writing									
Right	9.7	8.2	30	10.5	8.9	32	0.69	−3.6	5.2
Left	9.7	8.5	30	10.6	9.0	31	0.68	−3.6	5.4
Tapping dominant	41.0	14.0	40	43.0	13.5	40	0.51	−4.1	8.1

* Exact 95% confidence limits, α-stat minus pH-stat.

One patient (pH-stat) died intraoperatively due to technical difficulties in replacing a prosthetic valve, and another patient (pH-stat), who had no unusual degree of neuropsychologic impairment at postoperative testing, subsequently died from sepsis and multisystem failure. Two pH-stat patients died following discharge from the hospital (one from a stroke, one from unknown causes) before follow-up testing was performed. No new strokes or prolonged coma occurred among the remaining study patients. However, one pH-stat patient had recurrence of a neurologic deficit that had resolved following an old stroke. Three patients (all α-stat) refused postoperative testing; two patients who were tested postoperatively refused follow-up testing (one from each group); and two patients (one from each group) could not be located for follow-up testing. In all, 11 subjects did not complete the study: five from the α-stat group and six from the pH-stat group. Thus, data were available from 86 patients preoperatively, 82 patients postoperatively, and 75 patients at follow-up.

No significant differences were found between the CO_2 groups with respect to any of the cardiac measures (tables 3 and 4). Two variables (CK-MB fraction and defibrillations) were analyzed in both a continuous and dichotomous fashion.

Among the α-stat patients, 32 had CABG only and 12 had intracardiac operations; the corresponding numbers for pH-stat patients were 31 and 11. In this same group of patients, we previously found no significant differences on neuropsychologic testing between those having CABG and those having intracardiac surgery,[17] therefore, the two groups were combined for analysis of CO_2 effects. The pH-stat group had significantly better performance on one test preoperatively (tapping, dominant hand, $P = 0.03$, table 5). No significant differences were found between the pH-stat and α-stat groups in any of the test scores at postoperative testing (table 6) or at follow-up (table 7).

To screen the data for a possible trend that failed to reach statistical significance, the difference between the means of the summary change scores of the two CO_2 groups and their 95% confidence limits were plotted (fig. 1). The differences between the means of the two groups are scattered on either side of the line of zero difference; therefore, no trend is suggested favoring either group. As expected, the variability in the difference between groups (the length of the bars in fig. 1) was larger postoperatively than at follow-up.

Comparison of CO_2 group means in the foregoing analysis might have masked a situation in which a pre-

TABLE 7. Neuropsychologic Scores at Follow-up

	α-stat			pH-stat				Confidence Limits*	
	Mean	SD	N	Mean	SD	N	*P* Value	Lower	Upper
Shipley									
Vocabulary IQ	123.7	11.5	38	121.6	16.4	35	0.53	−8.7	4.5
Abstract IQ	96.7	18.7	37	98.7	23.8	35	0.70	−8.0	12.0
Conceptual IQ	82.9	15.3	37	85.2	19.0	35	0.56	−5.8	10.4
Trails									
A time	29.9	9.4	39	31.4	9.2	36	0.48	−2.8	5.8
B time	92.5	43.9	39	83.0	27.1	36	0.26	−27.5	7.5
WMS									
Verbal immediate	15.7	2.6	38	15.5	3.5	36	0.77	−1.6	1.2
Verbal delay	13.6	3.2	38	13.2	3.8	36	0.64	−1.8	1.0
No. of trials	3.0	1.3	38	2.8	1.4	36	0.77	−0.8	0.4
Visual immediate	8.5	3.2	38	9.6	3.4	36	0.16	−0.4	2.6
Visual delay	7.7	3.4	38	8.3	3.4	36	0.41	−0.9	2.1
SRT									
Trials	9.5	2.2	38	9.0	2.5	34	0.35	−1.6	0.6
Memories, last trial	9.1	1.3	38	9.2	1.3	34	0.68	−0.5	0.7
Sum recall	77.0	12.2	38	80.2	11.1	34	0.25	−2.3	8.7
Delayed recall	6.6	2.6	38	7.2	2.3	34	0.28	−0.6	1.8
Visual search time	173.0	93.0	34	175.2	96.6	33	0.92	−36.2	40.6
Digit vigilance time	109.4	24.3	39	114.5	32.4	36	0.45	−8.0	18.2
Digit symbol no. completed	50.6	12.2	39	48.6	11.2	36	0.45	−5.6	1.6
Aphasia									
Verbal	5.9	4.2	39	6.5	4.6	36	0.52	−3.8	5.0
Drawings	4.0	1.6	39	3.5	2.0	36	0.22	−1.4	0.4
Finger agnosia									
Right	0.3	0.5	29	1.3	3.8	28	0.16	−1.6	3.6
Left	0.4	1.0	28	1.3	3.8	28	0.27	−0.6	2.4
Fingertip no. writing									
Right	2.1	2.5	29	3.2	4.4	27	0.27	−0.8	3.0
Left	1.0	1.6	28	2.4	4.0	27	0.11	−0.2	3.0
Tapping dominant	46.5	7.4	39	48.5	10.1	36	0.32	−2.0	6.0

* Exact 95% confidence limits, α-stat minus *p*H-stat.

ponderance of the impaired patients occurred in one group or the other, despite a lack of difference between group means. To examine this possibility, we identified subsets of patients considered to exhibit impairment by various criteria: 1) 10 patients who showed a decline on at least one-half of the neuropsychologic tests from pre-

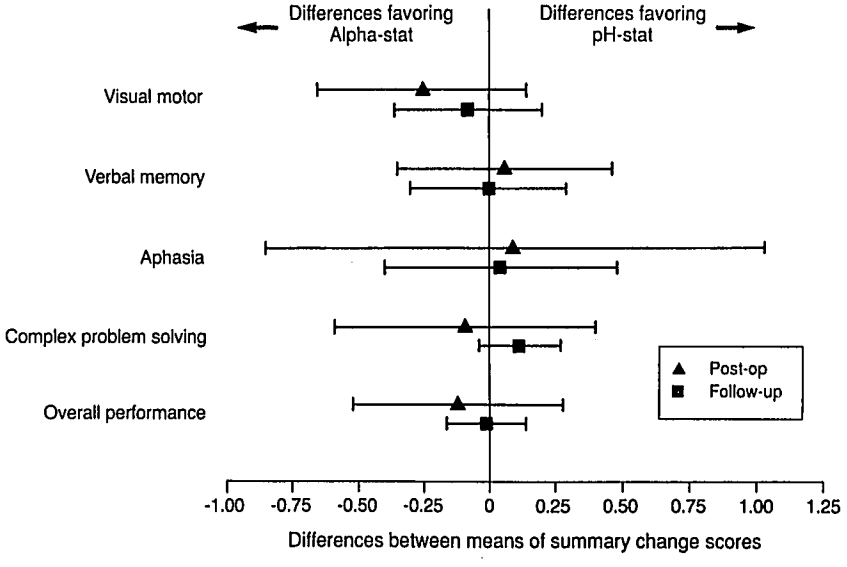

FIG. 1. Differences between mean summary change scores for α-stat and *p*H-stat patients from preoperation to postoperation (△) and from preoperation to follow-up (□). The bars indicate the 95% confidence intervals of the difference, and the vertical line represents zero difference between the groups.

TABLE 8. Comparison of Postoperation and Follow-up Summary Change Scores by TM50 Group

		TM50 < 100			TM50 ≥ 100			
		Mean	SD	N	Mean	SD	N	*P* Value
Visual motor	Postoperation	12.0	25.0	59	14.5	19.9	11	0.56
	Follow-up	0.9	22.7	54	6.0	11.5	10	0.25
Verbal memory	Postoperation	−16.2	22.4	58	−21.8	24.2	10	0.65
	Follow-up	5.1	13.9	52	5.0	8.3	10	0.63
Aphasia	Postoperation	0.2	1.8	59	0.6	1.0	10	0.24
	Follow-up	−0.3	0.9	54	0.5	0.8	9	0.01
Complex problem solving	Postoperation	1.0	1.2	51	0.9	0.6	11	0.79
	Follow-up	−0.2	0.4	47	−0.2	0.2	10	0.50
Overall performance	Postoperation	0.6	0.9	47	0.8	0.6	9	0.22
	Follow-up	−0.2	0.3	45	0.1	0.2	9	0.04

operation to follow-up; 2) 10 patients who had a decline in the overall impairment measure from preoperation to follow-up; 3) 7 patients who were clinically rated (by B.D.T. and D.B.C.) as performing poorly at both preoperation and follow-up testing; 4) 8 patients clinically rated as declining in functioning from preoperation to follow-up; and 5) 28 patients included in at least one of the aforementioned groups, taken together. (Seven subjects fell into two groups.) Two-by-two contingency tables were constructed for the CO_2 groups *versus* each of the outcome subsets discussed and analyzed by the Fisher's exact test. *P* values were 1.0, 0.26, 0.19, 1.0, and 0.81, respectively, indicating no association between the different groupings of impaired patients and the CO_2 group assigned.

Complete blood pressure data during bypass were available for 73 patients (34 α-stat and 39 *p*H-stat). Because no significant differences were observed between the CO_2 groups in mean blood pressure over the entire bypass run, TM50, or Lotime, the two groups were analyzed together. Thirteen patients had TM50 ≥ 100 mmHg · min. We compared their summary changes scores with those of the remaining 60 patients and found no significant differences at postoperative testing (table 8). However, at follow-up aphasia and overall performance were significantly different (table 8).

Because Stockard's threshold value for TM50 was arbitrary and because loss of information occurs in depicting these data in binary form, we also tested for associations between TM50 as a continuous variable and the summary change scores (table 9). No significant associations were found. We also constructed two-by-two contingency tables to test for association between the aforementioned five groupings of impaired patients and the occurrence of TM50 ≥ 100 mmHg · min. Respective *P* values were 1.0, 0.62, 0.50, 1.0, and 0.72, indicating no association.

Discussion

To our knowledge, this is the first investigation comparing the effects of α-stat *versus* *p*H-stat management of acid–base balance on the cerebral and cardiac outcome of patients undergoing hypothermic cardiopulmonary bypass. Despite the use of an extensive series of sensitive tests to measure neuropsychologic outcome and the use of several methods of data analysis, we have been unable to demonstrate any important differences in outcome using these two regimens. Generalized impairment in neuropsychologic performance was found in both groups at postoperative testing, but it essentially disappeared at follow-up.[17] At neither testing session did we detect any statistically significant differences between the performance of the α-stat and *p*H-stat groups. Furthermore, no trend is suggested favoring either CO_2 group in the confidence intervals of the individual tests at postoperation (table 6) or follow-up (table 7) or in the differences in the means of the summary change scores between CO_2 groups (fig. 1). Finally, patients considered to be impaired at follow-up by one criteria or another did not fall predominantly into either group. Although the four patients who died were all from the *p*H-stat group, three of the deaths were due to factors unrelated to bypass management and the fourth death was due to unknown causes and occurred after discharge from the hospital.

Intraoperative recordings were analyzed to determine whether hypotension during CPB might have been associated with neuropsychologic impairment. In an often-quoted paper, Stockard *et al.*[21] first suggested (but did not formally test for) an association between hypotension (defined by their hypotension index TM50 exceeding 100 mmHg · min) and an increased incidence and severity of cerebral injury. Interpretation of their results is difficult

TABLE 9. Pearson Correlation Coefficients of Association Between TM50 and Summary Change Scores

	Postoperation			Follow-up		
	r	*P*	N	*r*	*P*	N
Visual motor	−0.05	0.65	70	0.12	0.34	64
Verbal memory	−0.05	0.70	68	0.02	0.89	62
Aphasia	−0.08	0.54	69	0.15	0.23	63
Complex problem solving	−0.05	0.74	62	−0.07	0.60	57
Overall performance	0.01	0.95	56	0.19	0.17	54

because of confounding effects of increased age and CPB time in their cerebral deficit group.

More recently, Fish *et al.*[22] found a twofold increase in TM50 among prostacyclin-treated *versus* control patients; yet, they observed only one significant association between TM50 and postoperative neuropsychologic testing (Digit Span Backwards, $P = 0.05$). We found no difference in summary change scores between high- and low-TM50 patients by Stockard's criterion at postoperative testing. However, at follow-up both the aphasia and overall performance summary change scores were significantly different between TM50 groups. We believe that these follow-up changes are due to chance alone, inasmuch as they were not present at postoperative testing. With the large number of hypotheses tested in this study, the probability of one or two type I statistical errors is high. The lack of association between neuropsychologic scores and TM50, expressed as a continuous variable, or between high TM50 and the groupings of impaired patients further supports our belief that the difference in scores at follow-up is a chance occurrence. Our findings agree with those of Fish *et al.*,[22] Kolkka and Hilberman,[23] and Slogoff *et al.*,[24] although we did not experience TM50 as large as those that occurred in the first two of these studies.

With respect to cardiac outcome, the lack of significant differences between the CO_2 groups is in basic agreement with an earlier report.§§ Our finding of no difference in the duration of postoperative mechanical ventilation between CO_2 groups agrees with Murkin *et al.*[13] However, with our sample size, clinically significant differences in the duration of mechanical ventilation or ICU stay may have been missed. *A posteriori* statistical power calculations show that with 95% confidence and 80% power, the minimum detectable difference between the groups is 4 days of ICU stay or 8 h of mechanical ventilation.

In conclusion, this prospective randomized investigation found no significant differences in outcome between patients having α-stat *versus* *p*H-stat management during CPB at moderate hypothermia. Similarly, hypotension during CPB had no clinically important effect on neuropsychologic outcome. Moderate hypothermia is currently used for most adult cardiac surgery; therefore, these results should be widely applicable. However, most pediatric and some adult centers employ deeper hypothermia during CPB than we did, and our results cannot be extrapolated to those situations. Further research will be necessary to determine whether CO_2 management affects outcome when lower temperatures are employed.

§§ Foster RB, Zaidan JR, Mullins R, Steele M, Waller JL: Effect of Pa_{CO_2} management during CPB on post CPB cardiac performance (abstract). ANESTHESIOLOGY 61:A262, 1984

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