Risk factors for cognitive dysfunction after coronary artery bypass graft surgery in patients with type 2 diabetes

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Objectives: The mechanisms of postoperative cognitive dysfunction in patients with diabetes after coronary artery bypass grafting are not fully understood. We sought to determine which type 2 diabetes-related factors contributed to postoperative cognitive dysfunction at 7 days and 6 months after coronary artery bypass grafting.

Methods: One hundred eighty patients with type 2 diabetes who were scheduled for elective coronary artery bypass grafting were studied. As a control group, 100 patients without diabetes mellitus matched for age, sex, and educational level were examined. Hemodynamic parameters (arterial and jugular venous blood gas values) were measured during cardiopulmonary bypass. All patients underwent a battery of neurologic and neuropsychologic tests the day before surgery, 7 days after surgery, and 6 months after surgery.

Results: Age (odds ratio 1.5, 95% confidence interval 1.3-1.8, $P = .03$), presence of hypertension (odds ratio 1.8, 95% confidence interval 1.3-2.0, $P = .01$), jugular venous oxygen saturation less than 50% time (odds ratio 1.5, 95% confidence interval 1.1-2.0, $P = .045$), presence of ascending aorta atherosclerosis (odds ratio 1.5, 95% confidence interval 1.1-2.6, $P = .01$), diabetic retinopathy (odds ratio 2.0, 95% confidence interval 1.3-3.0, $P = .01$), and insulin therapy (odds ratio 2.0, 95% confidence interval 1.3-3.0, $P = .05$), were associated with cognitive impairment at 7 days. Insulin therapy (odds ratio 2.0, 95% confidence interval 1.3-3.8, $P = .01$), diabetic retinopathy (odds ratio 1.3, 95% confidence interval 1.2-2.9, $P < .01$), and hemoglobin A_{1c} (odds ratio 1.9, 95% confidence interval 1.3-3.1, $P = .047$) were associated with cognitive impairment at 6 postoperative months.

Conclusions: Insulin therapy, diabetic retinopathy, and hemoglobin A_{1c} were factors in cognitive impairment at 7 days and 6 months after coronary artery bypass grafting in patients with type 2 diabetes.

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Extant diabetes mellitus is a key factor associated with adverse postoperative neurologic outcomes after coronary artery bypass grafting (CABG).¹ Thourani and colleagues² reported that perioperative neurologic complications were more frequent among patients with diabetes than among patients without diabetes. However, the mechanisms of postoperative cognitive dysfunction in patients with diabetes after CABG are not fully understood.¹

Garcia and associates³ reported a higher mortality for women with insulin-treated diabetes than for patients with orally treated diabetes. Lawrie and colleagues⁴ noted that preoperative blood glucose level was an important predictor of late mortality among patients with diabetes. These findings suggest that the need for insulin treatment is one of the predictors of postoperative cognitive dysfunction in patients with diabetes. In contrast, Thourani and colleagues² reported that although perioperative neurologic complications were more frequent in patients with diabetes than in patients without diabetes, there was no difference in the incidence of perioperative neurologic complications between patients with type 1 and type 2 diabetes. Previously, there have been no reports examining the question of what diabetes-related factors other than the need for insulin treatment contribute to cognitive dysfunction after CABG in patients with type 2 diabetes.

Patients and Methods

This study was approved by the ethics committee of our institution, and written, informed consent was obtained from all patients. Between May 1994 and May 2000, a total of 199 patients with diabetes scheduled for elective CABG were approached, and 196 patients agreed to participate in this study. There was little change in anesthetic, surgical, and perfusion techniques during this period. Patients with type 2 diabetes mellitus were defined as those whose medical records showed a diagnosis of type 2 diabetes and medical treatment with antidiabetic therapy, such as dietary, oral, or insulin therapy. Duration of disease was defined as the duration from the time at which medical treatment was started. Some patients were the same as in other publications from our group.^{5,6} Patients with type 1 diabetes were excluded because their pathophysiology was quite different from that of patients with type 2 diabetes. We also studied 100 control patients without diabetes mellitus matched for age, weight, height, sex, and educational level. Table 1 shows the demographic data of the two groups.

Patients with a history of stroke or psychiatric illness were excluded. To rule out the possibility of the influence of renal failure or hepatic dysfunction on neurologic and neuropsychologic tests, we also excluded patients with renal disease (creatinine concentration >2.0 mg/dL) or active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 U/dL). All enrolled patients had undergone ophthalmologic examination for detection of diabetic retinopathy. Because glycosylated hemoglobin (HbA_{1c}, normal value, 4.5%-5.8%) is one of the indicators of diabetes control, all patients with diabetes were examined for preoperative HbA_{1c} level.

Anesthetic management was similar to that described in our previous study.⁵⁻⁷ Hemodynamic parameters and arterial and jugular venous blood gas values were measured at different times as described previously elsewhere.⁵⁻⁷

The target tympanic temperatures were from 34.5°C to 36.0°C. Below 34.5°C, a 34°C to 4°C difference between tympanic temperature and cardiopulmonary bypass (CPB) perfusate temperature was maintained during rewarming. The limit on maximal inflow temperature was set at 37.5°C. Phenylephrine infusions were used during CPB to maintain mean arterial pressure of 50 to 80 mm Hg.

TABLE 1. Demographic data from patients with type 2 diabetes and control patients

	Diabetes	Control
No.	180	100
Age (y, mean ± SD)	64 ± 11	67 ± 8
Height (cm, mean ± SD)	161 ± 11	164 ± 11
Weight (kg, mean ± SD)	64 ± 11	62 ± 10
Left ventricular ejection fraction (% mean ± SD)	58 ± 9	59 ± 8
Hypertension (No.)	136 (76%)	70 (70%)
β-Blocker (No.)	36	21
Angiotensin-converting, enzyme blocker (No.)	46	29
Calcium channel antagonist (No.)	52	20
Smoking (No.)	91 (51%)	50 (50%)
Male/female ratio	140:40	70:30
Peak perioperative glucose level (mg/dL, mean ± SD)	211 ± 41	220 ± 50
HbA _{1c} (% mean ± SD)	6.8 ± 3.6*	4.5 ± 0.8
Educational level (y, mean ± SD)	11.8 ± 2.2	12.3 ± 2.0
Preoperative hemoglobin (g/dL, mean ± SD)	12.5 ± 1.5	12.8 ± 1.9
Total CPB time (min, mean ± SD)	111 ± 31	119 ± 29
Aortic clamping time (min, mean ± SD)	99 ± 34	108 ± 22

**P* < .05 versus control; unpaired *t* test or χ^2 test was used for comparison between groups.

Blood glucose level during CPB was maintained between 100 and 200 mg/dL with insulin infusions. Pericardial aspirate was returned to the bypass circuit. Distal coronary anastomoses and proximal anastomoses were performed during a single aortic crossclamping.

Data analysis was later performed by an individual blinded to the groups to which patients belonged. The presence or absence of carotid artery stenosis in patients with or without diabetes was confirmed by preoperative ultrasonography and magnetic resonance imaging or angiography. The lesions found on ultrasonography and magnetic resonance imaging or magnetic resonance angiography were independently evaluated by two or three trained specialists who were blinded to preoperative risk factors and symptoms. The presence of carotid artery stenosis was defined as narrowing greater than 50%.⁸ We evaluated the presence of atherosclerotic lesions in the ascending aorta with intraoperative epiaortic ultrasonography during surgery in both diabetes and control groups. The presence of atherosclerotic lesions in the ascending aorta was defined as atherosclerotic lesions with at least 3.0 mm thickening with diffuse irregularities, large mobile or protruding atheromata, ulcerated plaques, or thrombi.⁸ To determine diabetic retinopathy status at the preoperative period, all fundus photographs were examined for the presence of diabetic retinopathy according to a modification of the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study grading scale.⁹ The presence of atherosclerotic lesions or diabetic retinopathy was determined by trained specialists, with intraobserver and interobserver validity ensured. Those who examined these lesions were unaware of each patient's intraoperative treatment assignment. Both examinations were performed for all pa-

tients. We defined integrated area under mean arterial pressure curve, change in tympanic temperature, and jugular venous oxygen saturation (SvO_2) less than 50% time as follows: integrated area under the curve for mean arterial pressure less than 50 mm Hg, tympanic temperature at the start of CPB minus tympanic temperature 20 minutes after the start of CPB, and time at which SvO_2 was less than 50%.

Neurologic and Neuropsychologic Assessments

All patients underwent a battery of neurologic and neuropsychologic tests administered by trained specialists, with intraobserver and interobserver validity ensured, the day before the operation and 7 days and 6 months after the surgery. The examiners who administered the cognitive tests were unaware of whether patients were in the control or diabetes group. Postoperative new stroke was defined according to both clinical assessment and either brain computed tomography or magnetic resonance imaging by trained specialists. The neuropsychologic portion of the study was designed in accordance with the consensus statements on the assessment of central nervous system disorders after cardiac surgery.¹⁰ Cognitive functioning was assessed with the following tests: (1) Mini-Mental State Examination, (2) Rey Auditory Verbal Learning Test, (3) Trail-Making Test (part A), (4) Trail-Making Test (part B), (5) Digit Span Forward, and (6) Grooved Pegboard.

Statistical Analysis

All data are expressed as mean $\pm$ SD. After the study was completed, sample size was evaluated. On the basis of our previous study, we considered a 20% reduction in cognitive dysfunction to be clinically important. The sample size provided 80% power to detect a 20% difference between patients with diabetes with insulin therapy and patients with diabetes without insulin therapy with a 5% probability of type I error. To obtain an indicator of outcome overall, significant impairment was defined as a decline from preoperative testing of more than 1 SD on more than 20% of test measures (at least 2 of 6). Differences in neuropsychologic tests between preoperative values and values obtained 7 days and 6 months after the operation were assessed with an analysis of covariance between diabetic and control groups. The data were examined with the Bartlett test to determine whether the variance was normally distributed between the groups. Univariate comparisons between subjects with and without cognitive impairment were performed with unpaired *t* test or χ^2 test for dichotomous variables and analysis of variance for ordered categoric and continuous variables. The latter analyses were performed nonparametrically when regression residuals suggested that the model fit was poor. Stepwise logistic regression was used to choose a best set of independent predictors of both short- and long-term cognitive impairment. Variables entered into the initial logistic models were those with a univariate probability value of $P < .2$. The final model included all variables with an independent significance level of $P < .1$. The quality of the fit of the logistic model was tested with the Hosmer-Lemeshow goodness-of-fit test. All calculations were performed on a Macintosh computer (Apple Computer, Inc, Cupertino, Calif) with SPSS (SPSS, Inc, Chicago, Ill) and StatView 5.0 (SAS Institute, Inc, Cary, NC) software packages.

Results

Table 1 shows the demographic data from the diabetes and control groups. There were no significant differences in demographic data between the two groups. The epiaortic scanning showed that 53 patients with diabetes had ascending aorta atherosclerosis and 12 control patients had ascending aorta atherosclerosis ($P < .05$).

We were unable to perform neuropsychologic assessments for 7 patients with diabetes (5 in insulin group and 2 in noninsulin group) 6 months after the operation, because these patients had died within 6 months after the surgery (mortality in insulin group 6% [5/83], mortality in noninsulin group 2% [2/104], $P < .05$). Three patients (excluding patients with major neurologic defects) had incomplete cognitive data, and 4 patients refused follow-up.

Major neurologic defects (defined as clinical evidence of focal cerebral infarction including hemiparesis, visual or gait disturbance, mental changes [confusion, agitation, inability to make contact with other people], or a combination of these) were observed in 9 patients after the operation (patients with diabetes with insulin therapy 5/86 [5.8%], patients with diabetes without insulin therapy 4/103 [3.9%], control group 1/100 [1.0%], $P = .19$).

We then performed neuropsychologic assessments for the 180 patients with diabetes. There was a significant difference in the incidence of cognitive impairment at 7 days between the control group and patients with diabetes (control 55/99 [55%], patients with diabetes 122/180 [68%], $P = .04$). In addition, there was a significant difference in the incidence of cognitive impairment at 6 months between the control group and patients with diabetes (control 11/99 [11%], patients with diabetes 51/180 [28%], $P = .0006$). Table 2 shows raw neurocognitive test scores at baseline and at 7 days and 6 months after the operation. Among patients with diabetes with cognitive impairment at 6 months, incidence of cognitive decline did not differ significantly between female and male patients (male 37/140 [26.4%], female 14/40 [35%], $P = .30$).

To assess whether elevated blood glucose level is a risk factor for cognitive impairment among patients with diabetes or whether patients with diabetes in general are at increased risk, we analyzed risk factors related to cognitive impairment at 7 days and 6 months in all patients. We found that age (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.0-1.5), SvO_2 less than 50% time (OR 1.2, 95% CI 1.0-1.3), CPB time (OR 1.1, 95% CI 1.0-1.2), hypertension (OR 1.7, 95% CI 1.0-1.9), ascending aorta atherosclerosis (OR 1.6, 95% CI 1.0-1.8), and diabetes (OR 2.2, 95% CI 1.6-3.3) were associated with cognitive impairment at 7 days. Diabetes (OR 2.5, 95% CI 1.4-3.6) was associated with cognitive impairment at 6 months. No relationship was found between a weighted average of blood glucose levels for

TABLE 2. Raw neurocognitive test scores at baseline and 7 days and 6 months, after the operation in the two groups

Test	Baseline	7 d	6 mo
Mini-Mental State Examination			
Diabetes	45.5 ± 2.9	43.0 ± 3.4	44.9 ± 2.8
Control	46.3 ± 2.5	43.0 ± 2.8	45.9 ± 2.6
Trail-Making Test (part A)			
Diabetes	45.9 ± 6.1	58.4 ± 11.1*†	51.1 ± 6.0*†
Control	45.4 ± 6.5	53.7 ± 9.1	47.5 ± 6.0
Trail-Making Test (part B)			
Diabetes	159.5 ± 22.2	192.9 ± 38.2*	170.0 ± 23.2
Control	163.5 ± 23.9	183.4 ± 42.4*	169.0 ± 28.1
Digit Span Forward			
Diabetes	9.3 ± 2.6	10.5 ± 3.2	9.7 ± 2.6
Control	9.4 ± 2.2	10.7 ± 3.6	10.7 ± 3.0
Grooved Pegboard			
Diabetes	22.3 ± 3.2	27.1 ± 4.9*†	23.4 ± 2.0
Control	21.9 ± 3.0	24.0 ± 4.7*	23.1 ± 3.0
Immediate recall			
Diabetes	40.7 ± 6.5	46.2 ± 4.3*†	45.0 ± 7.0*†
Control	39.9 ± 4.2	44.0 ± 2.7*	42.0 ± 5.0
Delayed recall			
Diabetes	23.4 ± 4.1	29.4 ± 3.0*	25.3 ± 2.4
Control	22.4 ± 3.9	27.3 ± 3.2*	24.9 ± 3.8

Values are mean ± SD. The immediate and delayed recall scores are derived from the Rey Auditory Verbal Learning Test.

* $P < .05$ versus baseline.

† $P < .05$ versus control.

TABLE 3. Analysis of patients with type 2 diabetes and cognitive impairment with and without insulin therapy at 7 days after operation and at 6 months after operation

	With insulin	Without insulin	<i>P</i> value
7 d (n = 122)			
No.	54/78 (69%)	68/102 (67%)	<.001
Fasting blood sugar (mg/dL, mean ± SD)	143 ± 33	132 ± 24	
HbA _{1c} (%; mean ± SD)	6.8 ± 1.8	6.1 ± 1.7	
Diabetic retinopathy (No.)	40/78 (60%)*	11/102 (4%)	<.001
Duration of disease (y, mean ± SD)	8.0 ± 5.0	7.5 ± 4.5	
6 mo (n = 51)			
No.	41/78 (80%)*†	10/102 (9.8%)	<.001
Fasting blood sugar (mg/dL, mean ± SD)	148 ± 30	122 ± 22	
HbA _{1c} (%; mean ± SD)	7.2 ± 0.9	5.2 ± 1.2	
Diabetic retinopathy (No.)	47/78 (60%)*†	4/102 (4%)	<.001
Duration of disease (y, mean ± SD)	8.7 ± 5.5	6.5 ± 4.2	

* $P < .05$ versus patients with diabetes without insulin therapy.

† $P < .01$ versus patients with diabetes without insulin therapy.

each 24-hour period and postoperative cognitive impairment at 7 days or 6 months in either the control or the diabetic group. At 7 days, there was no significant difference in incidence of cognitive decline, HbA_{1c}, or fasting blood sugar between patients with diabetes with insulin therapy and patients with diabetes without insulin therapy (Table 3). Incidence of diabetic retinopathy differed significantly between those receiving insulin and those not re-

ceiving insulin (Table 3). At 6 months, there was a significant difference in incidence of cognitive decline between patients with diabetes with insulin therapy (41/78; 80%) and patients with diabetes without insulin therapy (10/102, 9.8%, $P < .001$; Table 3), and there were significant differences in HbA_{1c}, fasting blood sugar, and incidence of diabetic retinopathy between those receiving insulin and those not receiving insulin (Table 3).

TABLE 4. Characteristics of patients with type 2 diabetes with and without cognitive dysfunction at 7 days and at 6 months

	No cognitive dysfunction	Cognitive dysfunction	P value
7 d			
No.	58	122	
Age (y, mean $\pm$ SD)	62 $\pm$ 8	69 $\pm$ 10	.09
Weight (kg, mean $\pm$ SD)	60 $\pm$ 11	66 $\pm$ 12	.19
Height (cm, mean $\pm$ SD)	159 $\pm$ 10	163 $\pm$ 7	.28
Hypertension (No.)	30/58 (52%)	106/122 (87%)	<.01
Smoking (No.)	29/58 (50%)	62/122 (51%)	.99
Female (%)	23%	25%	.36
Preoperative left ventricular ejection fraction (%; mean $\pm$ SD)	57 $\pm$ 9	54 $\pm$ 12	.29
Hemoglobin (g/dL, mean $\pm$ SD)	12.7 $\pm$ 1.0	12.4 $\pm$ 1.2	.51
CPB time (min, mean $\pm$ SD)	109 $\pm$ 20	116 $\pm$ 22	.66
Integrated area under mean arterial pressure curve (mean $\pm$ SD)	120 $\pm$ 19	127 $\pm$ 29	.26
Paco ₂ (mm Hg, mean $\pm$ SD)	36 $\pm$ 5	37 $\pm$ 5	.78
Svo ₂ less than 50% time (min, mean $\pm$ SD)	20.1 $\pm$ 9.4	46.2 $\pm$ 7.2	.02
Change in tympanic temperature ($^{\circ}$ C, mean $\pm$ SD)	1.1 $\pm$ 0.6	1.4 $\pm$ 0.9	.19
Ascending aorta atherosclerosis (No.)	10/58 (17%)	43/122 (35%)	.01
Carotid artery stenosis (No.)	5/58 (8.6%)	15/122 (12.3%)	.45
Diabetic retinopathy (No.)	11/58 (19%)	40/122 (33%)	.049
HbA _{1c} (%; mean $\pm$ SD)	6.1 $\pm$ 1.2	6.6 $\pm$ 1.2	.11
Duration of disease (y, mean $\pm$ SD)	6.3 $\pm$ 2.8	6.6 $\pm$ 4.3	.25
Fasting blood sugar (mg/dL, mean $\pm$ SD)	129 $\pm$ 16	137 $\pm$ 23	.34
Peak perioperative glucose level (mg/dL, mean $\pm$ SD)	199 $\pm$ 37	233 $\pm$ 48	.14
6 mo			
No.	129	51	
Age (y, mean $\pm$ SD)	63 $\pm$ 11	64 $\pm$ 10	.11
Weight (kg, mean $\pm$ SD)	62 $\pm$ 10	65 $\pm$ 13	.30
Height (cm, mean $\pm$ SD)	159 $\pm$ 10	160 $\pm$ 9	.68
Hypertension (No.)	98/129 (76%)	38/51 (75%)	.96
Smoking (No.)	63/129 (49%)	28/51 (55%)	.46
Female (%; mean $\pm$ SD)	20%	27%	.29
Preoperative left ventricular ejection fraction (%; mean $\pm$ SD)	59 $\pm$ 9	57 $\pm$ 11	.33
Hemoglobin (g/dL, mean $\pm$ SD)	12.3 $\pm$ 1.1	12.7 $\pm$ 0.9	.21
CPB time (min, mean $\pm$ SD)	106 $\pm$ 22	114 $\pm$ 22	.56
Integrated area under mean arterial pressure curve (mean $\pm$ SD)	122 $\pm$ 22	133 $\pm$ 31	.46
Paco ₂ (mm Hg, mean $\pm$ SD)	35 $\pm$ 4	37 $\pm$ 3	.38
Svo ₂ less than 50% time (min, mean $\pm$ SD)	24.0 $\pm$ 4.4	26.6 $\pm$ 8.9	.29
Change in tympanic temperature ($^{\circ}$ C, mean $\pm$ SD)	1.1 $\pm$ 0.5	1.0 $\pm$ 0.6	.39
Ascending aorta atherosclerosis (No.)	33/129 (26%)	20/51 (39%)	.075
Carotid artery stenosis (No.)	13/129 (10%)	7/51 (14%)	.49
Diabetic retinopathy (No.)	12/129 (9%)	39/51 (76%)	<.001
HbA _{1c} (%; mean $\pm$ SD)	5.1 $\pm$ 0.8	6.9 $\pm$ 1.0	<.001
Duration of disease (y, mean $\pm$ SD)	5.3 $\pm$ 2.6	7.6 $\pm$ 4.6	.09
Fasting blood sugar (mg/dL, mean $\pm$ SD)	113 $\pm$ 18	137 $\pm$ 33	.04
Peak perioperative glucose level (mg/dL, mean $\pm$ SD)	192 $\pm$ 33	231 $\pm$ 49	.09

Unpaired *t* test or χ^2 test was used for the comparison between groups.

Table 4 shows the characteristics of patients with diabetes with postoperative cognitive dysfunction and patients with no postoperative cognitive dysfunction at 7 days and 6 months. Presence of hypertension ($P < .01$), Svo₂ less than 50% time ($P = .02$), presence of ascending aorta atherosclerosis ($P = .01$), and diabetic retinopathy ($P = .049$)

differed significantly between patients with and without postoperative cognitive dysfunction at 7 days after the operation (Table 4). Diabetic retinopathy ($P < .001$), HbA_{1c} ($P < .001$), and fasting blood sugar ($P = .04$) differed significantly between patients with and without postoperative cognitive dysfunction at 6 months after the operation

(Table 4). At 7 postoperative days, cognitive impairment was associated with age (OR 1.5, 95% CI 1.3-1.8, $P = .03$), presence of hypertension (OR 1.8, 95% CI 1.3-2.0, $P = .01$), SvO_2 less than 50% time (OR 1.5, 95% CI 1.1-2.0, $P = .045$), presence of ascending aorta atherosclerosis (OR 1.5, 95% CI 1.1-2.6, $P = .01$), diabetic retinopathy (OR 2.0, 95% CI 1.3-3.0, $P = .01$), and insulin therapy (OR 2.0, 95% CI 1.3-3.0, $P = .05$; Table 5). At 6 postoperative months, cognitive impairment was associated with insulin therapy (OR 2.0, 95% CI 1.3-3.8, $P = .01$), diabetic retinopathy (OR 2.1, 95% CI 1.2-2.7, $P < .01$), and HbA_{1c} (OR 1.9, 95% CI 1.3-3.1, $P = .047$; Table 5). Insulin therapy (OR 2.1, 95% CI 1.4-3.5, $P = .01$), diabetic retinopathy (OR 2.4, 95% CI 1.4-2.9, $P < .01$), and HbA_{1c} (OR 2.0, 95% CI 1.5-3.3, $P = .042$) were associated with postoperative cognitive impairment (Table 5).

Discussion

The principal findings of this study are as follows: (1) Cognitive dysfunctions was more evident and frequent among patients with type 2 diabetes than in patients without diabetes at 7 days and at 6 months after CABG. (2) Hypertension, reduced SvO_2 , and ascending aorta atherosclerosis were associated with short-term cognitive dysfunction in patients with type 2 diabetes, whereas, insulin therapy, diabetic retinopathy, and HbA_{1c} were associated with cognitive impairment at 6 months after CABG among patients with type 2 diabetes.

Many studies have found that diabetes mellitus is associated with a worse long-term outcome after CABG.^{1,8,11} Newman and associates¹¹ reported that diabetes was one of the key variables predicting major perioperative neurologic events. Hogue and colleagues⁸ showed that diabetes was an independent predictor of delayed stroke. These reports led us to examine the mechanisms associated with postoperative adverse neurologic events in patients with diabetes.

One possible cause of postoperative cognitive dysfunction in patients with diabetes mellitus is impaired cerebrovascular circulatory and vasodilatory reserves.¹²⁻¹⁴ Croughwell and colleagues¹² reported that the cerebral blood flow (CBF) of their diabetic group was constant despite an increase in temperature from 27°C to 37°C, in contrast to an 83% increase in CBF in the control group. They concluded that patients with type 2 diabetes receiving insulin had impaired CBF autoregulation. In a series of studies,^{13,14} we found that patients with diabetes had a reduced cerebral oxygenation, as estimated by SvO_2 , during CPB, and that reduced SvO_2 during CPB was associated with cognitive dysfunction in elderly patients.⁷ There is controversy regarding the results of studies of cerebrovascular carbon dioxide reactivity in patients with diabetes. Dandona and associates¹⁵ examined the reactivity of CBF, challenging with 5% carbon dioxide in 59 patients with diabetes, and

TABLE 5. Independent predictors of cognitive impairment at 7 days or 6 months after cardiac surgery in patients with type 2 diabetes

Variables	OR	95% CI	P value
All cognitive impairment			
HbA_{1c} (%)	2.0	1.5-3.3	.042
Diabetic retinopathy	2.4	1.4-2.9	<.01
Insulin therapy	2.1	1.4-3.5	.01
Short-term cognitive impairment			
Age	1.5	1.3-1.8	.03
Hypertension	1.8	1.3-2.0	.01
SvO_2 less than 50% time	1.5	1.1-2.0	.045
Ascending aorta atherosclerosis	1.5	1.1-2.6	.01
Diabetic retinopathy	2.0	1.3-3.0	.01
Insulin therapy	2.0	1.3-3.0	.05
Long-term cognitive impairment			
HbA_{1c} (%)	1.9	1.3-3.1	.047
Diabetic retinopathy	2.1	1.2-2.7	<.01
Insulin therapy	2.0	1.3-3.8	.01

found that patients with diabetes had diminished cerebrovascular reserve. In contrast, Kawata and coworkers¹⁶ reported that the relative values of carbon dioxide reactivity in patients with diabetes were equivalent to those of the control group during isoflurane anesthesia. In an animal study by Sieber and colleagues,¹⁷ 4 months of hyperglycemia increased CBF and cerebral metabolic rate for oxygen. They speculated that the effects of diabetes mellitus on the cerebral vasculature were complicated by a host of factors, including diabetic microangiopathy, atherosclerosis, hypertension, renal disease, and chronic hyperglycemia, and concluded that it was likely that many of the reported abnormalities in CBF physiology were the results of diabetic vascular disease, rather than an effect of hyperglycemia.

This study is the first to show that insulin therapy, HbA_{1c} , and retinopathy are associated with cognitive impairment at 6 months after CABG. Although we cannot explain why these factors are related to cognitive impairment, prolonged hyperglycemia may be a factor. Pallas and associates¹⁸ noted that hyperglycemia leads to impaired vascular function though changes in endothelial cell function. The pathway that appears most affected by the diabetic state is that of nitric oxide. Loss of this pathway is accompanied by loss of response to $Paco_2$ and lack of autoregulation related to flow-pressure relationships. The United Kingdom Prospective Diabetes Study¹⁹ reported that intensive blood glucose control substantially decreases the risk of microvascular complications. Our results indicate that high HbA_{1c} and diabetic retinopathy reflect poorly controlled diabetes, suggesting that severity of microangiopathy in patients with diabetes with high HbA_{1c} is higher than that in patients with diabetes with normal HbA_{1c} .²⁰ Ono and colleagues²¹ reported that retinal circulation may be an indi-

cator of cerebrovascular circulation, because the retina develops from the forebrain. In a previous study,²² we reported that cerebral vasodilatory response to hypercapnia was impaired in patients with diabetes with retinopathy relative to patients with diabetes without retinopathy and found that HbA_{1c} was positively related to impaired cerebrovascular carbon dioxide reactivity. Stratton and associates²³ reported that in patients with type 2 diabetes the risk of diabetic complications, such as macrovascular and microvascular disease, was strongly associated with previous hyperglycemia. This implies that the primary cause of microvascular disease is chronic hyperglycemia itself and that poorly controlled blood sugar induces disturbed cerebrovascular microcirculation, which may have adverse effects on postoperative cognitive function. Among our 51 patients with diabetes with cognitive impairment 6 months after the operation, those who received insulin therapy had a disease duration of almost 9 years, whereas those who did not receive insulin therapy had a disease duration of 6.5 years. Type 2 diabetes may be present for prolonged periods before diagnosis, and as many as 50% of patients may have significant disorders, such as diabetic microvascular complications, without clinical symptoms before the disease is diagnosed.²⁴ Elevated HbA_{1c} and diabetic retinopathy are indicators of poor control of diabetes and are also indicators of the duration of type 2 diabetes, because most patients with type 2 diabetes have the condition diagnosed several years after onset.

The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study¹⁹ demonstrated that tight glucose control reduces risk of mortality. Moreover, Ohkubo and coworkers²⁵ reported that intensive blood glucose therapy prevented progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent type 2 diabetes mellitus. Our results indicate that intensive preoperative blood glucose therapy may be important for reduction of the incidence of postoperative cognitive impairment.

Study Limitations

We did not identify any relationship between postoperative cognitive dysfunction and ascending aorta atherosclerosis or carotid artery stenosis at 6 months after surgery. Several reports have shown that ascending aorta atherosclerosis and carotid artery stenosis represent major factors associated with cognitive dysfunction.^{1,11} The incidence of ascending aorta atherosclerosis or carotid artery stenosis among our patients may have been too small to detect a relationship. In addition, there is controversy regarding the definition of a significant level of narrowing.^{8,26,27} The North American Symptomatic Carotid Endarterectomy Trial²⁶ report defined carotid artery stenosis as narrowing greater than 70%. In contrast, White and coworkers²⁷ defined carotid artery ste-

nosis as narrowing greater than 60%. Further study is needed to determine the relationship between postoperative cognitive dysfunction and ascending aorta atherosclerosis or carotid artery stenosis.

Because we selected normothermic CPB, we strictly controlled tympanic temperature during the CPB period in this study. Hypothermia is known to protect against brain ischemia, and hyperthermia is known to be a risk factor of postoperative cognitive dysfunction.²⁸ We cannot rule out the possibility that different results would be obtained for hypothermic CPB.

In this study we excluded patients with major neurologic outcome and incomplete data from cognitive function analysis. This may have had some effects on our results. Rasmussen and associates²⁹ recommended in a review article that tests with missing data not be used for evaluation of cognitive function simply because such missing data can not be substituted in any reasonable way.

We followed the recommendations for neuropsychologic testing and the definition of postoperative cognitive dysfunction provided in the consensus statements on the assessment of central nervous system disorders.¹⁰ The test used in this study is widely accepted for evaluation of postoperative cognitive function. There have been many problems regarding definitions of postoperative cognitive dysfunction. Rasmussen and associates²⁹ reported in a review of the literature that postoperative cognitive function has been extensively researched but is a difficult matter to evaluate. In addition, they found large differences in methodology between studies, including test batteries, interval between sessions, the end points analyzed, statistical methods, and definitions of neuropsychologic defects and postoperative cognitive dysfunction.

Our study provided 80% power to detect a 20% difference between patients with diabetes with insulin therapy and patients with diabetes without insulin therapy, with a 5% probability of type I error. Determining the significance of a 10% difference between two groups would have required a total sample size of 297,654.

Conclusion

In this study, there were no differences in peak perioperative glucose level between the diabetes and control groups or between patients with and without cognitive dysfunction. Insulin therapy, diabetic retinopathy, and HbA_{1c} were associated with cognitive impairment 6 months after CABG. Recent studies^{24,30} indicate that aggressive glucose control in both patients with and without diabetes can improve survival without excessive consequences related to hypoglycemia. This suggests that maintaining the "tight" glyce-mic control reported by Van Den Berghe and colleagues³⁰ (maintaining blood glucose in the range of 80-110 mg/dL) during the perioperative period can improve postoperative

cognitive function in patients undergoing cardiac surgery. Further study should help to clarify the optimal blood glucose concentration and the role of maintaining euglycemia in patients undergoing cardiac surgery.

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