Cognitive Decline after Delirium in Patients Undergoing Cardiac Surgery

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ABSTRACT

Background: Delirium is common after cardiac surgery and has been associated with morbidity, mortality, and cognitive decline. However, there are conflicting reports on the magnitude, trajectory, and domains of cognitive change that might be affected. The authors hypothesized that patients with delirium would experience greater cognitive decline at 1 month and 1 yr after cardiac surgery compared to those without delirium.

Methods: Patients who underwent coronary artery bypass and/or valve surgery with cardiopulmonary bypass were eligible for this cohort study. Delirium was assessed with the Confusion Assessment Method. A neuropsychologic battery was administered before surgery, at 1 month, and at 1 yr later. Linear regression was used to examine the association between delirium and change in composite cognitive Z score from baseline to 1 month (primary outcome). Secondary outcomes were domain-specific changes at 1 month and composite and domain-specific changes at 1 yr.

Results: The incidence of delirium in 142 patients was 53.5%. Patients with delirium had greater decline in composite cognitive Z score at 1 month (greater decline by −0.29; 95% CI, −0.54 to −0.05; $P = 0.020$) and in the domains of visuoconstruction and processing speed. From baseline to 1 yr, there was no difference between delirious and nondelirious patients with respect to change in composite cognitive Z score, although greater decline in processing speed persisted among the delirious patients.

Conclusions: Patients who developed delirium had greater decline in a composite measure of cognition and in visuoconstruction and processing speed domains at 1 month. The differences in cognitive change by delirium were not significant at 1 yr, with the exception of processing speed. **(ANESTHESIOLOGY 2018; 129:406-16)**

DELIRIUM is a common complication after cardiac surgery that may occur in more than 50% of patients.[1] Delirium has been associated with long-term mortality,[2] perioperative morbidity,[3] increased duration of hospitalization,[4] and higher costs.[4] Delirium has further been associated with accelerated cognitive decline in a range of populations, including critically ill patients in the intensive care unit,[5] patients undergoing surgery,[6] and patients with dementia.[7] However, common methodologic limitations to these reports, including insensitive delirium assessment, limited neuropsychologic evaluation, and short follow-up, have restricted the characterization of the relationship between delirium and cognitive decline.

Postoperative cognitive change has been a subject of intense focus for patients undergoing surgery, particularly those undergoing cardiac surgery with cardiopulmonary bypass (CPB).[8] A previous study in U.S. patients undergoing cardiac

What We Already Know about This Topic

- Cardiac surgery is associated with cognitive decline and postoperative delirium
- The relationship between postoperative delirium and cognitive decline after cardiac surgery is unclear

What This Article Tells Us That Is New

- The development of postoperative delirium is associated with a greater degree of cognitive decline 1 month after cardiac surgery
- The development of postoperative delirium is not a predictor of cognitive decline 1 yr after cardiac surgery

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 389. This article has an audio podcast. This article has a visual abstract available in the online version. The association of delirium and cognitive change was examined in a small number of patients and presented as an abstract at the 2014 meeting of the American Society of Anesthesiologists on October 14, 2014, in New Orleans, Louisiana. The abstract was selected for the session "Best Abstracts: Clinical Science."

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surgery identified delirium as an important risk factor for cognitive decline at 1 month but not 1 yr after cardiac surgery.[9] However, cognitive assessment was measured with the Mini-Mental State Examination, a brief cognitive screening tool with known limitations.[10] A recent study using a more robust neuropsychologic battery also found cognitive decline at 1 month but not at 1 yr among delirious patients with the Confusion Assessment Method[11] and derivatives in a European cardiac surgery population.[12] In this study, the delirium incidence was substantially lower than in other studies,[1,9,13] due to either reduced sensitivity or operationalization of the delirium assessment. Our primary goal was to examine the association between delirium and cognitive change at 1 month after cardiac surgery in a U.S. population, using a sensitive delirium assessment and an expanded neuropsychologic battery. As secondary outcomes, we also examined cognitive change at 1 yr and domains of cognitive change at both time points. Our primary hypothesis was that delirium would be associated with decline in cognition at 1 month after cardiac surgery.

Materials and Methods

Institutional Review Board and Consent

This study was approved by the Johns Hopkins Institutional Review Board (Baltimore, Maryland) and written informed consent was obtained from all participants. Institutional review board approval of the parent study was granted on August 4, 2009. This manuscript adheres to the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines.

Study Design and Patients

This was a prospective observational study, nested in an ongoing trial that randomized patients to blood pressure targets during CPB based on cerebral autoregulation monitoring *versus* the usual practice in which these targets are empirically chosen.[14,15] The parent trial was registered as NCT00981474. As the purpose of the current study was to evaluate the relationship between postoperative delirium and cognitive changes, and not to test hypotheses about blood pressure management during CPB, data from both groups were combined. Data on a portion of these patients have been reported previously in an article examining hospital resources after delirium, but the primary hypothesis of this study has not previously been evaluated or reported.[4] Patients were included in this study if they were undergoing primary or reoperative coronary artery bypass and/or valve surgery and/or aortic root surgery that required CPB and who were at high risk for neurologic complications (stroke or encephalopathy) as determined by a Johns Hopkins risk score composed of history of stroke, presence of carotid bruit, hypertension, diabetes, and age that generally excluded patients in the lowest quartile of risk.[16] Exclusion criteria were renal failure, hepatic dysfunction, non-English speaking, contraindications to magnetic resonance imaging (*e.g.*, pacemaker), and emergency surgery.

Perioperative Care

Patients received standard institutional monitoring, including radial arterial blood pressure monitoring. General anesthesia was induced with fentanyl, midazolam, and/or propofol and was maintained with isoflurane and a nondepolarizing muscle relaxant. CPB was performed with a nonocclusive roller pump and a membrane oxygenator, and the circuit included a 40 μm or smaller arterial line filter. Nonpulsatile flow was maintained between 2.1 and 2.4 $l \cdot min^{-1} \cdot m^{-2}$. Patients were managed with alpha-stat pH management. Rewarming was based on institutional standards with a goal of maintaining nasal pharyngeal temperature less than 37°C. After surgery, patients were sedated with a propofol infusion until they qualified for tracheal extubation or for 24 h after surgery. Patients requiring more than 24 h of mechanical ventilation received an infusion of fentanyl and/or midazolam.

Delirium Assessment (Primary Exposure) and Data Collection

Delirium was assessed with rigorous methodologies, including the Confusion Assessment Method[11] and Confusion Assessment Method for the Intensive Care Unit.[17] All research staff participating in delirium assessments were masked to randomization group in the parent study. The Confusion Assessment Method was performed in person by formally trained research assistants and included a structured cognitive examination (Mini-Mental State Examination,[18] Digit Span Forwards/Backwards, and timed Months-of-the-Year Backwards). Research assistants also queried the patient, nurses, families, and medical records for evidence of delirium. Findings from this overall assessment were used to determine diagnosis of delirium. For intubated patients in the intensive care unit, the validated Confusion Assessment Method for the Intensive Care Unit was used, which allows delirium assessment of nonverbal patients. For days on which patients could not be assessed in person due to either patient or staff availability, a validated chart review was used (sensitivity of 74% and specificity of 83%).[19] Coma was assessed with the Richmond Agitation Sedation Scale, with a score of −4 or −5 indicating coma. Patients who were comatose on all assessments (regardless of sedation medication) were classified as having coma in this analysis.

The once-daily delirium assessments were limited to the first four postoperative days because of evidence that more than 90% of delirium occurs within this time.[20] For the analysis, delirium was defined as any Confusion Assessment Method, Confusion Assessment Method for the Intensive Care Unit, or chart review positive assessment during hospitalization.

Delirium assessors underwent formal training by a psychiatrist (K.J.N.), who is an expert in delirium diagnosis. Training included readings, videos, and delirium assessments of 10 patients with subsequent discussion. During the study, delirium assessors and the psychiatrist team member conducted co-ratings of patients every 2 weeks. Finally, research assistants met with delirium experts 1 to 2 times/month to discuss delirium assessments of nonstudy patients, to ensure consistent

methods and judgment. During the study, we measured agreement among researchers, and kappa statistics were between 0.7 and 0.8, which is consistent with substantial agreement.[4]

Neuropsychologic Battery

Neuropsychologic testing was generally performed within 2 weeks of surgery and then 4 to 6 weeks and 1 yr after surgery. The tests assessed a number of cognitive domains known to be affected by cardiac surgery.[21,22] The test battery consisted of the Rey Auditory Verbal Learning Test,[23] Rey Complex Figure Test,[24] Controlled Oral Word Association Test,[25] Symbol Digits Modalities Test,[26] Trail Making Tests A and B,[27] and Grooved Pegboard Test.[28] The tests were grouped into the following cognitive domains *a priori* by a neuropsychologist (V.K.): attention (Rey Auditory Verbal Learning Test I correct), memory (Rey Auditory Verbal Learning Test V correct, Rey Auditory Verbal Learning Test IX correct), visuoconstruction (Rey Complex Figure Test copy trial score), verbal fluency (Controlled Oral Word Association Test letters F, A, S), processing speed (Symbol Digits Modalities Test correct, Trail Making Test A), executive function (Trail Making Test B), and fine motor speed (Grooved Pegboard, dominant and nondominant hand).

Statistical Analysis

The primary exposure was any positive delirium assessment. As a sensitivity analysis, we also added two patients who were comatose at all assessments and thus could not be assessed for delirium. The primary cognitive outcome was change in a composite cognitive Z score from baseline to 1 month after surgery, as described and used previously by our group.[29,30] This score was obtained by first calculating Z scores for individual tests at each testing time point with the mean and SD of baseline tests of all patients in the parent study. Timed tests were multiplied by "−1" so that higher scores represented better performance. Next, individual test Z scores were averaged at each time point and renormalized to generate a composite cognitive Z score. Finally, the difference in composite Z scores was calculated for each interval of interest. This method was also employed to calculate domain-specific cognitive scores, which we examined in exploratory analyses. Previous work has considered changes in composite Z scores of 0.3 to 0.5 to be clinically significant, based on epidemiologic data.[31,32]

The sample size for this nested cohort study was determined by the number of patients with available delirium and cognitive assessments. Originally, we had calculated that 126 patients would be necessary to show a difference in change in composite cognitive Z score from baseline to 1 month with 80% power, assuming an improvement in the nondelirious group of 0.1 ± 0.4 and a decline in the delirious group of −0.1 ± 0.4. Subsequently, in a *post hoc* analysis using actual data, we also calculated that 126 patients would provide approximately 80% power to detect a difference in cognitive Z score of 0.5 SD between delirium groups at 1 yr.

Baseline patient characteristics were compared with Student's *t* tests, Wilcoxon rank sum tests, and chi-square tests. Cognitive change was examined with linear regression. As advocated by others,[33] we did not account for learning effect or surgery, since we were interested in the difference between two groups of patients, both of whom underwent surgery and had the opportunity for learning effect. Accounting for learning effect may be most important with dichotomous cognitive outcomes, such as studies classifying patients according to a threshold of postoperative cognitive dysfunction. However, in our study, we examined continuous change in cognition without dichotomous categorizations. Variables for which to adjust were considered on the basis of our review of the literature and before examining the data and included age, sex, race, education, and logistic EuroSCORE (European system for cardiac operative risk evaluation). We also examined characteristics from table 1 for potential inclusion into the model, but we did not include diabetes to avoid inclusion of potentially mediating effects in the logEuroSCORE. This analytic plan was based on previous methodology used by our research group[29] and was agreed upon before accessing the data. In the adjusted model with change in cognition as the outcome, we chose not to adjust for baseline cognitive scores due to the potential for bias that could be introduced.[34] Using PROC MI in SAS (SAS Institute, Inc., USA), we conducted a sensitivity analysis to account for missing 1-yr follow-up cognitive data with multiple imputation. Missing data (10 datasets) were imputed with age, sex, race, education, logEuroSCORE, and baseline and 1-month cognitive data. The regression model was fit with PROC MIANALYZE (SAS Institute, Inc.). A *P* value of less than 0.05 was considered significant for all analyses.

Results

Patients

Data were available from 142 patients with delirium assessments and neuropsychologic testing. Figure 1 shows a patient flow diagram. The number of patients completing follow-up neuropsychologic testing at 1 month was 140 and at 1 yr was 108. The reasons for missing follow-up testing at 1 month were patient refusal (2), and at 1 yr were study withdrawal (13), lost to follow-up (20, of which 10 were subsequently noted to be alive at the time of 1-yr follow-up), and death (1). Delirium was diagnosed in 76 (53.5%) patients. Confusion Assessment Method assessments were performed in 69% of assessments, with the remaining patients being comatose (1.4%), assessed with Confusion Assessment Method for the Intensive Care Unit (3%), or assessed with chart review (27%). The characteristics of patients by delirium status are shown in table 1. The mean ± SD age of the patients was 70 ± 8 yr; 75% were male and 81% were of European descent. Notably, there was no difference in patient age between patients with and without delirium. Patients with delirium had a lower composite cognitive Z score (mean ± SD) at baseline (−0.19 ± 0.92) than patients who did not develop delirium (0.20 ± 1.09; $P = 0.025$). Delirium incidence was not different among patients with available

Table 1. Patient Characteristics

	Entire Cohort (N = 142)	No Delirium (n = 66)	Delirium (n = 76)	*P* Value
Age (yr), mean (SD)	70 ± 8	70 ± 7	70 ± 8	0.790*
Sex, n (%)				0.096†
Male	107 (75.4)	54 (81.8)	53 (69.7)	
Female	35 (24.6)	12 (18.2)	23 (30.3)	
Race, n (%)				0.407‡
European descent	115 (81.0)	56 (84.9)	59 (77.6)	
African-American	19 (13.4)	8 (12.1)	11 (14.5)	
Other	8 (5.6)	2 (3.0)	6 (7.9)	
Education (yr), median (IQR)	16 (12–17)	16 (12–17)	16 (12–17)	0.612‡
Comorbidities, n (%)				
Previous stroke	18 (13.0)	9 (14.3)	9 (12.0)	0.691†
Hypertension	132 (93.0)	60 (90.9)	72 (94.7)	0.374†
Atrial fibrillation	34 (23.9)	16 (24.2)	18 (23.7)	0.938†
Infarction	39 (27.5)	18 (27.3)	21 (27.6)	0.962†
COPD	11 (7.8)	4 (6.2)	7 (9.2)	0.546‡
Obstructive sleep apnea	30 (21.3)	15 (23.1)	15 (19.7)	0.629†
Tobacco (current)	11 (7.8)	5 (7.7)	6 (7.9)	0.964†
Diabetes	64 (45.1)	24 (36.4)	40 (52.6)	0.0520†
Anemia	60 (42.6)	28 (42.4)	32 (42.7)	0.977†
Logistic EuroSCORE, median (IQR)	4.5 (2.3–9.0)	4.3 (2.2–7.3)	4.8 (2.5–10.4)	0.196‡
Surgery, n (%)				0.408‡
CAB	66 (46.5)	29 (43.9)	37 (48.7)	
CAB + valve	24 (16.9)	10 (15.2)	14 (18.4)	
Valve	50 (35.2)	27 (40.9)	23 (30.3)	
Other	2 (1.4)	0 (0)	2 (2.6)	
Cardiopulmonary bypass duration (min), median (IQR)	115 (89–146)	118 (90–145)	114 (85.5–153.5)	0.872‡
Aortic cross-clamp duration (min), median (IQR)	73 (57–94)	72.5 (59–91)	73 (53–100)	0.995‡
Baseline depression score, median (IQR)	7 (3–11)	5 (3–10)	8 (4–11)	0.157‡

**P* values are calculated by Student's *t* test. †*P* values are calculated by chi-square test. ‡*P* values are calculated by Wilcoxon rank sum test. §*P* values are calculated by Fisher exact test.

CAB = coronary artery bypass; COPD = chronic obstructive pulmonary disease; EuroSCORE = European system for cardiac operative risk evaluation; IQR = interquartile range.

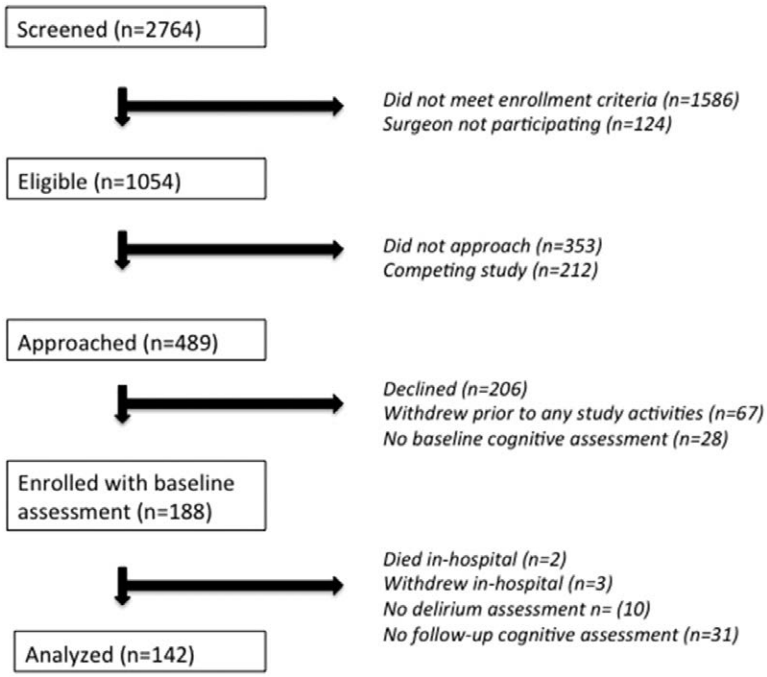

Fig. 1. Patient flow chart.

Table 2. Composite Cognitive Z Scores and Interval Changes in Scores at Baseline, 1 Month, and 1 Yr after Surgery

	All Patients (N = 142)	No Delirium (n = 66)	Delirium (n = 76)	Difference between Delirium Groups*		
				B Coefficient	95% CI	*P* Value
Cognitive Z score, mean (SD)						
Baseline (n = 142)	−0.009 ± 1.02	0.20 ± 1.09	−0.19 ± 0.92	−0.34	−0.64 to −0.04	0.025
1 month (n = 140)	−0.13 ± 1.17	0.23 ± 1.01	−0.45 ± 1.21	−0.67	−1.01 to −0.33	< 0.001
1 yr (n = 108)	−0.24 ± 0.94	−0.04 ± 0.94	−0.42 ± 0.90	−0.36	−0.69 to −0.03	0.033
Change in cognitive Z score, mean (SD)						
Baseline to 1 month (n = 140)	−0.11 ± 0.72	0.035 ± 0.46	−0.23 ± 0.87	−0.29	−0.54 to −0.05	0.020
Baseline to 1 yr (n = 108)	−0.33 ± 0.62	−0.27 ± 0.54	−0.39 ± 0.67	−0.13	−0.37 to 0.11	0.298
1 month to 1 yr (n = 106)	−0.22 ± 0.66	−0.28 ± 0.48	−0.15 ± 0.80	0.13	−0.14 to 0.39	0.348

*Adjusted for age, sex, race, education, and logistic EuroSCORE.

cognitive data at 1 yr (53% [57/108]) compared with those patients missing data at 1 yr (56% [19/34]; $P = 0.752$).

Composite Cognitive Z Scores

Baseline and Follow-up. Composite cognitive Z scores by delirium status at baseline, 1 month, and 1 yr after surgery are shown in table 2 and graphically in figure 2. As expected, composite cognitive Z scores were lower in patients with delirium than in those without delirium at all individual time points: baseline (−0.19 ± 0.92 *vs.* 0.20 ± 1.09; $P = 0.025$), 1 month (−0.45 ± 1.21 *vs.* 0.23 ± 1.01; $P < 0.001$), and 1 yr after surgery (−0.42 ± 0.90 *vs.* −0.04 ± 0.94; $P = 0.033$).

Change in Cognitive Scores. However, as shown in table 2 and figure 2, the decline in composite cognitive Z score from baseline to 1 month after surgery was greater among patients with delirium than among patients without delirium (greater decline by −0.29; 95% CI, −0.54 to −0.05; $P = 0.02$). This model was adjusted for age (−0.002; 95% CI, −0.02 to 0.02; $P = 0.818$), sex (male *vs.* female: 0.009; 95% CI, −0.29 to 0.31; $P = 0.951$), race (black *vs.* white: −0.15; 95% CI, −0.53 to 0.22; $P = 0.422$; other *vs.* white: 0.13; 95% CI, −0.41 to 0.66; $P = 0.638$), education (more than 16 yr *vs.* less than 12 yr: 0.15; 95% CI, −0.49 to 0.80; $P = 0.634$; 12 to 16 yr *vs.* less than 12 yr: 0.30; 95% CI, −0.32 to 0.91; $P = 0.342$), and logistic EuroSCORE (0.008; 95% CI, −0.01 to 0.03; $P = 0.444$). In contrast, from baseline to 1 yr after surgery, there was no difference in adjusted decline from baseline in composite cognitive Z score by delirium status ($P = 0.298$). Using multiple imputation to account for missing cognitive data predominantly at 1 yr, we found similar results, with delirious patients having greater cognitive decline at 1 month (−0.29; 95% CI, −0.52 to −0.06; $P = 0.015$) but not at 1 yr (−0.11; 95% CI, −0.33 to 0.12; $P = 0.14$). Because cognitive change is nonlinear during the first year after surgery, we also examined cognitive change from 1 month to 1 yr and found no difference by delirium status. In a sensitivity analysis, we found no change in the results if patients with coma were included in the delirium group.

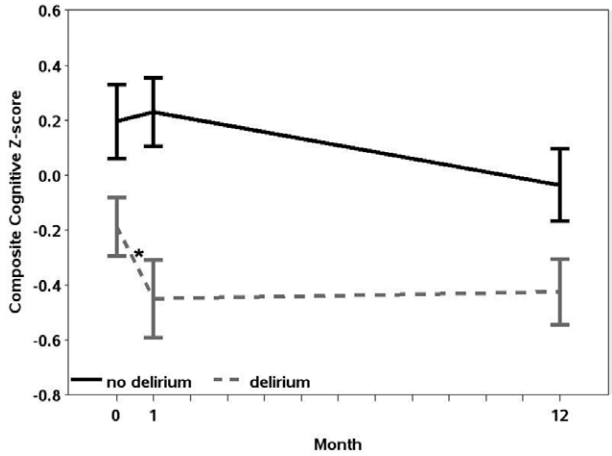

Fig. 2. Composite cognitive Z scores by delirium status at baseline, 1 month, and 1 yr after cardiac surgery. Error bars refer to SD. There is a significant difference in decline from baseline to 1 month in patients with delirium compared to patients without delirium as indicated by the *asterisk*.

Domain-specific Cognitive Z Scores

Domain-specific cognitive Z scores by delirium status were examined in exploratory analysis and are shown at baseline, 1 month, and 1 yr after surgery in table 3 and figure 3. Visual inspection of domain-specific trajectories of cognitive Z scores generally demonstrated a decline across domains from baseline to 1 month. However, adjusted decline was only greater in the delirium group than in the nondelirium group in the domains of visuoconstruction (greater decline by −0.45; 95% CI, −0.78 to −0.13; $P = 0.007$) and processing speed (greater decline by −0.53; 95% CI, −0.96 to −0.09; $P = 0.018$). From baseline to 1 yr, adjusted decline in the domain of processing speed was greater in the delirium group than in the nondelirium group (greater decline by −0.58; 95% CI, −0.95 to −0.22; $P = 0.002$). There were no other cognitive domains that showed differences in cognitive trajectories from baseline to 1 yr by delirium status. There were also no statistical differences in recovery of cognition from 1 month to 1 yr by delirium status. The predominant pattern from 1 month to 1 yr was greater recovery in

Table 3. Domain-specific Cognitive Z Scores and Interval Changes in Scores at Baseline, 1 Month, and 1 Yr after Surgery

	No Delirium (n = 66)	Delirium (n = 76)	Difference between Delirium Groups*		
			B Coefficient	95% CI	*P* Value
Attention					
Cognitive Z score					
Baseline	0.23 ± 1.05	−0.04 ± 1.00	−0.28	−0.61 to 0.05	0.095
1 month	0.28 ± 0.97	−0.09 ± 0.96	−0.40	−0.72 to −0.08	0.015
1 yr	−0.0001 ± 0.48	0.15 ± 1.50	0.20	−0.24 to 0.64	0.360
Change in cognitive Z score					
Baseline to 1 month	0.05 ± 0.94	−0.02 ± 1.05	−0.09	−0.43 to 0.26	0.621
Baseline to 1 yr	−0.32 ± 0.74	0.06 ± 1.67	0.49	−0.01 to 1.00	0.056
1 month to 1 yr	−0.22 ± 0.71	0.22 ± 1.60	0.49	−0.007 to 0.98	0.053
Memory					
Cognitive Z score					
Baseline	0.42 ± 1.70	0.23 ± 1.55	−0.29	−0.83 to 0.24	0.284
1 month	0.46 ± 1.74	−0.02 ± 1.61	−0.52	−1.06 to 0.02	0.060
1 yr	0.12 ± 1.69	0.12 ± 1.52	−0.04	−0.68 to 0.59	0.889
Change in cognitive Z score					
Baseline to 1 month	0.03 ± 1.04	−0.24 ± 1.35	−0.22	−0.64 to 0.20	0.294
Baseline to 1 yr	−0.36 ± 1.60	−0.33 ± 1.33	0.06	−0.54 to 0.65	0.846
1 month to 1 yr	−0.30 ± 1.32	−0.02 ± 1.36	0.26	−0.28 to 0.80	0.335
Visuoconstruction					
Cognitive Z score					
Baseline	0.11 ± 0.88	0.11 ± 0.92	0.08	−0.20 to 0.35	0.579
1 month	0.18 ± 0.75	−0.19 ± 1.19	−0.37	−0.70 to −0.04	0.025
1 yr	−0.01 ± 0.75	−0.21 ± 0.92	−0.13	−0.45 to 0.19	0.427
Change in cognitive Z score					
Baseline to 1 month	0.08 ± 0.86	−0.35 ± 0.96	−0.45	−0.78 to −0.13	0.007
Baseline to 1 yr	−0.13 ± 0.76	−0.37 ± 0.78	−0.23	−0.54 to 0.08	0.142
1 month to 1 yr	−0.21 ± 0.87	−0.15 ± 0.77	0.09	−0.24 to 0.42	0.608
Verbal fluency					
Cognitive Z score					
Baseline	0.93 ± 2.71	−0.07 ± 2.22	−0.90	−1.71 to −0.08	0.031
1 month	0.96 ± 2.80	−0.14 ± 2.36	−1.01	−1.84 to −0.17	0.019
1 yr	0.84 ± 2.78	−0.39 ± 2.30	−1.13	−2.12 to −0.14	0.026
Change in cognitive Z score					
Baseline to 1 month	0.03 ± 1.44	−0.03 ± 1.63	−0.06	−0.60 to 0.47	0.814
Baseline to 1 yr	−0.33 ± 1.76	−0.54 ± 1.66	−0.22	−0.91 to 0.46	0.523
1 month to 1 yr	−0.40 ± 1.55	−0.37 ± 1.72	0.01	−0.66 to 0.68	0.976
Processing speed					
Cognitive Z score					
Baseline	0.66 ± 1.69	0.27 ± 1.42	−0.30	−0.73 to 0.13	0.174
1 month	0.72 ± 1.40	−0.11 ± 1.87	−0.83	−1.36 to −0.31	0.002
1 yr	0.37 ± 1.40	−0.43 ± 1.66	−0.76	−1.29 to −0.22	0.006
Change in cognitive Z score					
Baseline to 1 month	0.06 ± 0.81	−0.42 ± 1.51	−0.53	−0.96 to −0.09	0.018
Baseline to 1 yr	−0.19 ± 0.93	−0.82 ± 0.98	−0.58	−0.95 to −0.22	0.002
1 month to 1 yr	−0.38 ± 0.96	−0.52 ± 1.01	−0.13	−0.53 to 0.27	0.519
Executive function					
Cognitive Z score					
Baseline	0.37 ± 0.67	0.09 ± 0.87	−0.24	−0.48 to 0.01	0.063
1 month	0.36 ± 0.58	−0.19 ± 1.22	−0.51	−0.83 to −0.19	0.002
1 yr	0.20 ± 0.86	−0.13 ± 1.04	−0.37	−0.72 to −0.01	0.044
Change in cognitive Z score					
Baseline to 1 month	−0.03 ± 0.41	−0.23 ± 0.86	−0.18	−0.42 to 0.06	0.139
Baseline to 1 yr	−0.12 ± 0.55	−0.32 ± 0.90	−0.24	−0.54 to 0.07	0.127
1 month to 1 yr	−0.11 ± 0.60	−0.19 ± 0.89	−0.14	−0.44 to 0.17	0.380
Motor speed					
Cognitive Z score					
Baseline	0.30 ± 0.63	0.09 ± 0.70	−0.23	−0.46 to 0.01	0.065
1 month	0.20 ± 0.90	−0.04 ± 0.89	−0.23	−0.57 to 0.11	0.189
1 yr	−0.11 ± 1.42	0.06 ± 0.60	0.17	−0.26 to 0.59	0.435
Change in cognitive Z score					
Baseline to 1 month	−0.08 ± 0.53	−0.13 ± 0.63	−0.07	−0.31 to 0.17	0.558
Baseline to 1 yr	−0.16 ± 0.48	−0.07 ± 0.47	0.04	−0.17 to 0.25	0.714
1 month to 1 yr	−0.22 ± 1.00	0.01 ± 0.54	0.28	−0.06 to 0.62	0.110

*Adjusted for age, sex, race, education, and logistic EUROScore.

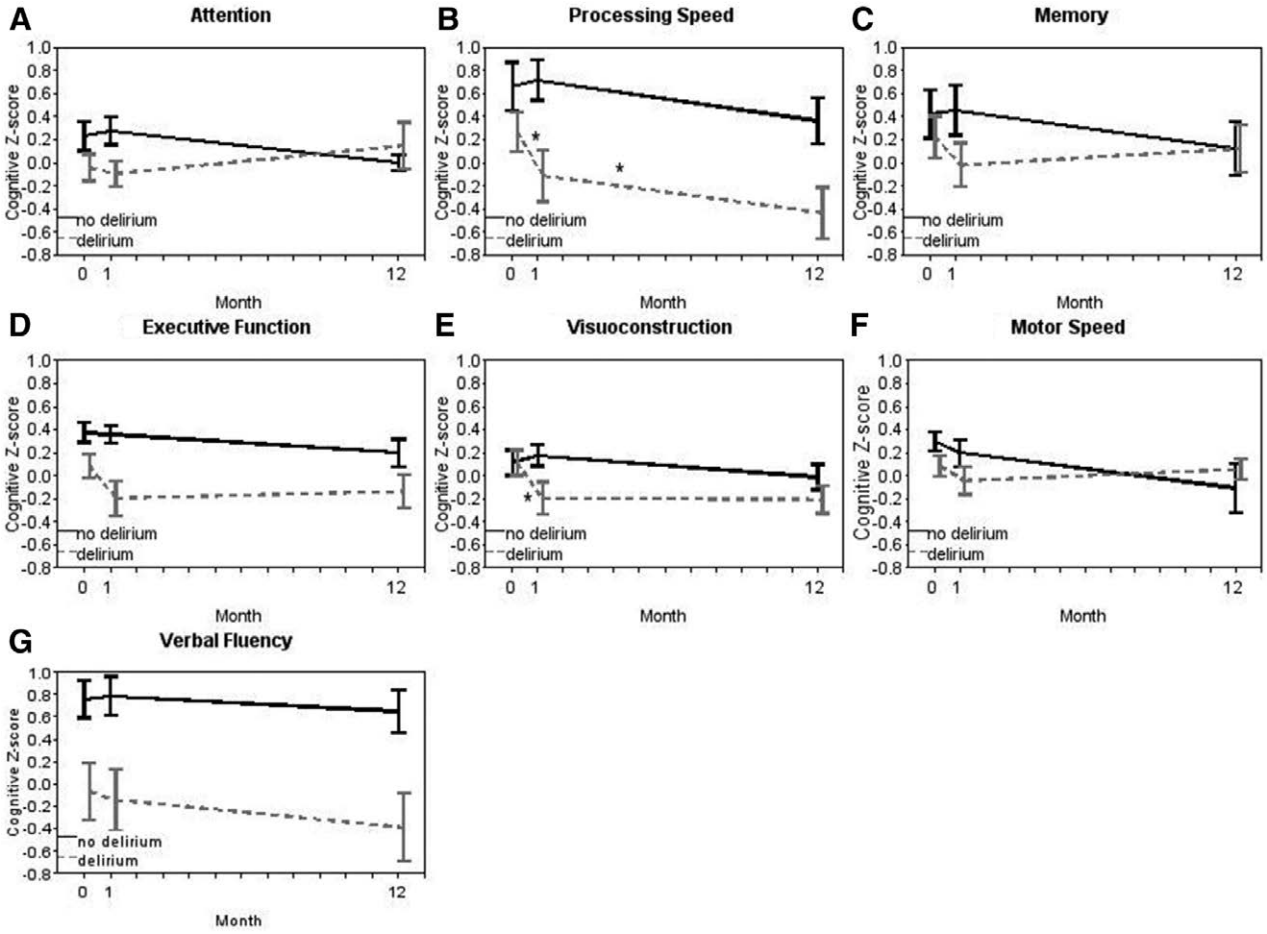

Fig. 3. Domain-specific cognitive Z scores by delirium status at baseline, 1 month, and 1 yr after cardiac surgery. Error bars refer to SD. There is a significant difference, indicated by the *asterisk*, in decline between patients with delirium and patients without delirium in the domains of processing speed and visuoconstruction from baseline to 1 month and in the domain of processing speed from baseline to 1 yr.

the delirium group, with the exception of the domains of processing speed and verbal fluency, which did not fit this general pattern and showed similar trajectories between the delirium and nondelirium groups.

Discussion

The results of this study demonstrate that patients with delirium have greater decline from baseline in a composite measure of cognitive function 1 month after surgery than patients without delirium. In exploratory analysis, the domains of psychomotor speed and visuoconstruction were most negatively affected by the presence of postoperative delirium. One year after surgery, patients with delirium had a greater decline in processing speed than patients without delirium. There were no differences in decline from baseline in any other specific cognitive domain, or in the composite measure of cognitive function, by delirium status at 1 yr after surgery.

Our results from this study support findings from other studies suggesting that delirium after surgery is associated with nonlinear changes in postoperative cognition.[9,35] In particular, delirium appears to be associated with "delayed neurocognitive recovery," a term used in new nomenclature to describe early postoperative cognitive change.[36] Interestingly, nonlinear changes in cognition after cardiac surgery have been consistently described over the past two decades,[8,37] most prominently by Newman *et al.*, who reported an incidence of cognitive decline of 24% at 6 months and 42% at 5 yr after cardiac surgery.[8] Our results add to this literature by clarifying a role for delirium in explaining heterogeneity in cognitive trajectories. In particular, our results confirm the results of Sauër *et al.*,[12] who examined a European cohort of patients undergoing cardiac surgery with a robust neuropsychologic battery. These investigators found that patients with delirium had greater cognitive decline at 1 month but not 1 yr after cardiac surgery compared to patients without delirium. Importantly, the incidence of delirium was only 12.5% in their study, likely due to operationalization of the delirium assessment and/or reduced sensitivity.[38] Our study extends the results of Sauër *et al.* by using a more sensitive delirium examination and showing similar findings. Thus, the association of delirium and postoperative cognitive

change is not limited to the most severe or clinically obvious forms of delirium, an observation that emphasizes the importance of screening for and preventing even mild cases of postoperative delirium.

Saczynski *et al.*[9] also reported in a study of 225 cardiac surgery patients that cognitive decline measured with Mini-Mental State Examination was greater among patients with delirium in the weeks to months after surgery than among patients without delirium. By 1 yr there was recovery of Mini-Mental State Examination scores in each group, with the delirium group still having lower scores (P = 0.06). Although frequently used as a global measure of cognitive function, there is no ideal cognitive test for all populations, and the Mini-Mental State Examination can be limited by a ceiling effect (*i.e.*, it may not detect cognitive decline in patients who are high performing at baseline), limited sensitivity to change in some populations, and limited ability to examine specific cognitive domains.[10] In this study, the incidence of delirium was 46% (similar to the incidence in our study). The consistency of our results, and those of Saczynski *et al.*[9] and Sauër *et al.*,[12] demonstrate that the association of delirium and cognitive change is robust to heterogeneous methods of delirium and cognitive assessment. Furthermore, in a noncardiac surgery population screened for delirium with clinical tools, delirium was associated with a greater likelihood of developing mild cognitive impairment or dementia at follow-up.[39]

It is important to note, however, that the association between delirium and cognitive decline has not been consistent across all studies and surgical populations. For example, in a secondary analysis of 850 patients from Franck *et al.*,[40] delirium after noncardiac surgery did not affect the incidence of postoperative cognitive dysfunction at 1-week and 3-months follow-up, although delirium in the immediate postanesthesia period and within 7 days was associated with worse cognitive outcomes. In this study, postoperative cognitive dysfunction was classified as a binary diagnosis, which may have limited the power to detect a difference between groups and contributed to the negative results of the study.

The majority of studies assessing the effects of postoperative delirium on cognition have followed patients only to 1 yr after surgery. However, participants enrolled in the Successful Aging after Elective Surgery study[35] underwent neuropsychologic testing up to 3 yr postoperation. In that noncardiac surgery population, a similar biphasic pattern in cognition was seen with steeper cognitive decline in patients with delirium from baseline to 1 month than in patients without delirium. At 1 yr, there was recovery in both groups with no difference in cognitive decline by delirium status. Subsequently, slopes of cognitive change diverged, with delirious patients having accelerated cognitive decline. These results suggest that it may be important to measure cognitive outcomes longer than 1 yr after surgery, and thus our findings of no difference in cognition at 1 yr by delirium group cannot be extrapolated to longer-term outcomes.

Understanding the mechanism for associations between delirium and cognitive decline is critically important, and several possibilities exist. Delirium might be a "stress test" for the brain, identifying patients at high risk for subsequent cognitive decline and who might benefit from rehabilitation strategies. Obtaining preoperative cognitive trajectories would help illuminate this question; however, these data are difficult to obtain before surgery. In hospitalized patients with dementia, longitudinal studies of cognition have shown accelerated cognitive decline after delirium, suggesting a potential contribution from delirium.[7]

Another explanation for the relationship between delirium and cognitive decline is that perioperative insults may contribute independently to both delirium and longer-term cognitive decline. For example, neuroinflammation[41,42] and changes in cerebral blood flow[43,44] have been hypothesized to contribute to short- and long-term brain dysfunction and to provide plausible mechanisms for the observed findings of this and other studies.[45] Finally, the ramifications of delirium (such as decreased mobility[46] or altered sleep–wake cycles[47]) might lead to subsequent cognitive change. Understanding the pathophysiologic basis for the observed association between delirium and cognitive decline will be crucial for developing targeted strategies for treatment and prevention.

Our findings of differences in the specific cognitive domains are exploratory but may be hypothesis generating for future studies. Processing speed is an important component of cognitive tasks, which are critical to navigate the postsurgical recovery period. Impairments in processing speed have been correlated with impaired functional status,[48] including activities of daily living such as managing finances, nutrition, and medications.[49] Observational studies have suggested that delirium is associated with changes in white matter integrity,[50] and further that white matter integrity is associated with measures of processing speed,[51] thus providing a potential mechanistic hypothesis for our observed results. The changes in processing speed may also suggest a subcortical injury consequence from delirium. In contrast, there were no differences by delirium status in memory or attention, which may involve more cortical processes. These findings may influence the design of future neuroimaging and molecular imaging studies to examine mechanisms for cognitive decline after delirium. Visuoconstruction refers to the coordination of fine motor skills with spatial abilities, and may substantially impact tasks such as driving and writing.[52] Our findings may be particularly important for older adults, in whom the preservation of these tasks is critically important. Interestingly, our findings corroborate those of previous results,[8] which demonstrated short-term decline in the domains of processing speed and visuoconstruction after cardiac surgery, and suggest that delirium may provide one explanation.

Strengths of this study include rigorous assessment of delirium and a comprehensive neuropsychologic battery with assessment of domain-specific change. As a sensitivity analysis, we also examined coma and delirium together to account for the contribution of severe brain dysfunction, in

accord with previous methodology.[53] We were able to adjust for several important confounding variables. However, there are limitations to consider in interpreting the results. First, the study was observational by necessity, which makes it difficult to attribute causality, and further studies are needed to assess the extent to which the relationship between delirium and cognitive change reflects association, mediation, or causation. Second, we did not measure cognitive trajectories before surgery, so we cannot exclude that delirious patients were already declining in cognition. Third, our delirium methods are generally sensitive, so they may identify cases of delirium that would not be clinically evident. Fourth, we followed patients up to 1 yr after surgery but do not have cognitive data at later time points. Our sample size may also be underpowered to detect differences by group smaller than 0.5 SD at 1 yr. Finally, our analyses with regard to domains of cognition are exploratory given the multiple comparisons and should be considered hypothesis generating.

The results of this study support a growing body of literature suggesting that delirium is associated with cognitive decline 1 month after cardiac surgery. Preservation of cognitive status in the weeks to months after cardiac surgery is an important patient-centered goal to facilitate prompt return to presurgical functional status, such as living independently with normal social engagement. With the exception of processing speed, there is recovery to normal in most cognitive domains by 1 yr after surgery. Further studies are needed to clarify longer-term cognitive outcomes and to elucidate mechanisms for these findings in patients undergoing cardiac surgery.

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Competing Interests

Dr. Brown and Dr. Hogue consulted for and received grant support from Medtronic (Minneapolis, Minnesota) in unrelated areas, and Dr. Nomura has received funding from Medtronic in unrelated areas. Dr. Neufeld has received research funding from Hitachi Medical Corporation (Twinsburg, Ohio). The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Tintype and Chloroform Inhaler of Confederate Surgeon J. J. Chisolm, *Not Chisholm*

One of the most misspelled names in medical history is that of John Julian Chisolm, M.D. (1830 to 1903). He was not Julian John Chisholm…. Fortunately, this image (*left*), reconstructed from a tintype in the collection of the Wood Library-Museum, has captured his visage more accurately than medical literature has recorded Chisolm's name. An 1850 graduate of the Medical College of the State of South Carolina (MCSSC), Chisolm treated Civil War wounded from the Battle of Fort Sumter and then served as a Confederate Surgeon in both Virginia and South Carolina. From 1867 through 1872, Dr. Chisolm served as dean at the MCSSC and then the University of Maryland School of Medicine. As illustrated not in Chisolm's masterwork, *A Manual of Military Surgery, for the Use of Surgeons in the Confederate Army*, but in a Tiemann catalog, his namesake Chisolm inhaler (*right*) spared use of chloroform, with which the Confederacy was undersupplied. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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