DELIRIUM AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

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Background Postoperative delirium is associated with increased mortality. Patients undergoing transcatheter aortic valve replacement are at risk for delirium because of comorbid conditions.

Objective To compare the incidence, odds, and mortality implications of delirium between patients undergoing transcatheter replacement and patients undergoing surgical replacement.

Methods The Richmond Agitation-Sedation Scale and the Confusion Assessment Method for the Intensive Care Unit were used to assess arousal level and delirium prospectively in all patients with severe aortic stenosis who had transcatheter or surgical aortic valve replacement at an academic medical center. Multivariable logistic regression was used to determine the relationship between procedure type and occurrence of delirium. Cox regression was used to assess the association between postoperative delirium and 6-month mortality.

Results A total of 105 patients had transcatheter replacement and 121 had surgical replacement. Patients in the transcatheter group were older (median age, 81 vs 68 years; $P<.001$) and had more comorbid conditions (median Charlson Comorbidity Index, 3 vs 2; $P<.001$). Patients in the transcatheter group also had lower incidence (19% vs 21%; $P=.65$) and odds of delirium developing (odds ratio, 0.4; 95% CI, 0.2-0.9; $P=.03$). Delirium was independently associated with a 3-fold higher mortality by 6 months (hazard ratio, 3.4; 95% CI, 1.3-8.8; $P=.01$).

Conclusions Delirium occurs in at least 1 in 5 patients after transcatheter or surgical aortic valve replacement. Delirium is less likely to develop in the transcatheter group but is associated with higher mortality in both groups. (*American Journal of Critical Care.* 2017;26:e58-e64)

D elirium is a prevalent dysfunction characterized by disturbances in level of consciousness and cognition and is associated with increased morbidity and mortality in both medical and surgical patients.[1-3] Observed morbidities include longer hospitalization, decrease in cognitive and functional status, complications after surgery, and elevated health care costs.[2-5] Factors that increase risk for delirium include advanced age, previous cognitive impairment, frailty and functional limitations, metabolic disturbances, and renal impairment. An individual patient's risk increases as the number of risk factors increases.[3] Additionally, factors such as use of restraints, administration of psychoactive medications, and lack of sleep can predispose patients to delirium.[6,7]

Without routine use of a delirium-monitoring instrument, delirium can easily go undiagnosed.[8] The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), a validated tool that can be reliably used by nonpsychiatrists to diagnose delirium, even in patients treated with mechanical ventilation, is now recommended by the Society of Critical Care Medicine for use in critically ill patients.[9]

Reported rates of delirium after cardiothoracic surgery are from 3% to 70%.[10-12] Risk factors for delirium in this situation include advanced age, decreased left ventricular ejection fraction, increased body mass index, and male sex. Adverse outcomes for patients with delirium after cardiothoracic surgery are similar to those observed in general medical and surgical patients.[10-12]

Transcatheter aortic valve replacement (TAVR) is an available option for patients with severe aortic stenosis whose operative risk precludes traditional surgical valve replacement (SAVR).[13] The incidence of postoperative delirium is 3% to 32%[14,15] in TAVR patients and up to 35% in SAVR patients.[15] However, no research has been published on the risk factors for delirium among TAVR and SAVR patients that account for the differences in age and comorbid conditions that often determine the choice of valve replacement options or on the effect of delirium on outcomes in these 2 different populations of patients.

Materials and Methods

The institutional review board at Vanderbilt University Medical Center, Nashville, Tennessee, approved the study with a waiver of consent because of the observational design. Adult patients who underwent TAVR or SAVR between July 1, 2011 and July 31, 2012 at the medical center were included in the study. Data were obtained from the Society of Thoracic Surgeons database for SAVR and an institution-specific database for TAVR patients. All patients were admitted after the procedure to the Vanderbilt cardiovascular intensive care unit (CVICU), a tertiary level critical care unit managed by a multidisciplinary team of physicians, pharmacists, and critical care nurses accustomed to providing care to TAVR and SAVR patients.

Data Collection

Data on patients who died within 24 hours of valve replacement or had persistent coma after the procedure were excluded from the analysis.

Baseline demographics and information on preexisting conditions were obtained from the medical records. Assessments done as part of routine preoperative medical care for TAVR or SAVR included laboratory testing and assessment of left ventricular systolic function by using echocardiography. The severity of comorbid illness was calculated by using

> Postoperative delirium is an underrecognized complication with important implications for outcomes.

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Step 1: Sedation and level of arousal assessment with the RASS

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive, vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact to *voice* (≥10 seconds)	Verbal stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

If score is -4 or -5, then **Stop** and **Reassess** patient at later time

If score is >-4 (-3 through +4) then **Proceed to Step 2**

Step 2: Delirium assessment with the CAM-ICU

Feature 1: Acute onset of mental status changes or a fluctuating course

and

Feature 2: Inattention

and

Feature 3: Disorganized thinking   OR   **Feature 4:** Altered level of consciousness
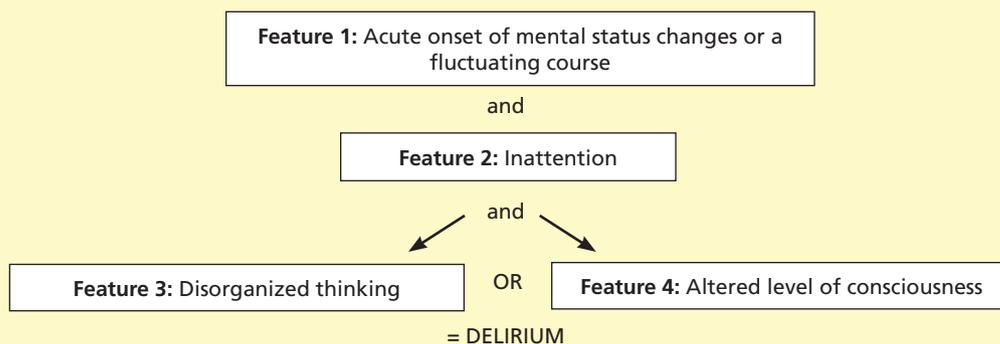
= DELIRIUM

Figure 1 A 2-step process of delirium assessment. The Richmond Agitation-Sedation Scale (RASS) is used to assess the level of sedation and arousal (step 1). If the patient can respond to verbal stimulation (RASS level ≥-3), then delirium is assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU; step 2).

Adapted with permission from http://www.icudelirium.org/delirium/monitoring.html (E. Wesley Ely).

the Charlson Comorbidity Index.[16] Procedure-specific information such as the vascular access for the procedure, blood loss, and type and dose of sedative and anesthetic agents used for SAVR and TAVR were collected from anesthesia reports. Postoperative medications and laboratory data were obtained from medical records. A daily cardiovascular Sequential Organ Failure Assessment score[16] was calculated for each patient to account for hemodynamic changes and vasopressor support during the CVICU stay.

As part of routine care, CVICU nurses determined patients' neurological status by using the Richmond Agitation-Sedation Scale (RASS) to assess arousal and the CAM-ICU to assess delirium and recorded the results in the medical record (Figure 1). The RASS is a valid and reliable 10-point scale with scores from +1 to +4 for levels of agitation through combativeness, 0 for an alert and calm state, and -1 to -5 for

successive levels of depressed arousal or coma.[17] The CAM-ICU results were documented as "unable to assess" if patients had a RASS score of -4 or -5, signifying a comatose state. The CAM-ICU value was considered positive for delirium if patients had a RASS score of -3 or greater and had an acute change or fluctuation in mental status plus inattention and either disorganized thinking or an altered level of consciousness.[9,18] Patients' level of arousal determined by using the RASS and the presence of delirium determined by using the CAM-ICU were noted in the electronic medical record a minimum of every 12 hours while patients remained in the CVICU and were recorded for up to 3 days postoperatively or until discharge from the unit, whichever came earlier. Vital status at 30 days and 6 months after discharge from the hospital and date of death (if applicable) were determined via medical records or the Social

Security Death Index if not already known at the time of discharge from the hospital.

Statistical Analysis

Descriptive statistics are presented as medians and interquartile ranges for continuous variables and as percentages for categorical variables. The Wilcoxon rank sum test and the Pearson χ^2 test were used to compare the baseline characteristics between patients who had TAVR and patients who had SAVR. Delirium was considered present if at least 1 CAM-ICU assessment was positive during the study period.

Multivariable logistic regression was used to assess the association between the procedure types (TAVR vs SAVR) and the occurrence of postoperative delirium, with adjustments made for age at procedure time, preoperative ejection fraction, Charlson Comorbidity Index, and intraoperative midazolam dose. The area under the receiver operating characteristic curve was 0.644 (95% CI, 0.558-0.729), and the model likelihood ratio χ^2 was 9.7 with 5 degrees of freedom ($P = .08$), indicating a good model fit. Survival models (Cox regression) were used to assess the association between postoperative delirium and 6-month mortality, with adjustments for age and procedure type. A sensitivity analysis was used to analyze the relationship between presence of delirium and time to death, further incorporating the Charlson Comorbidity Index in addition to the age and procedure type in the model just described. All tests were 2-tailed, with a significance level set at $\alpha = .05$. All statistical analyses were performed by using R statistical software, version 2.15.1.

Results

A total of 233 patients met the inclusion criteria. Of these, 7 patients were excluded; 4 died perioperatively and 3 had persistent coma for 3 days after the procedure. Thus, the final sample consisted of 226 patients: 105 had TAVR (46%) and 121 had SAVR (54%). Of the TAVR patients included, the majority had TAVR via a transfemoral approach; 16 had a direct aortic approach.

Demographic data and baseline characteristics are presented in Table 1. TAVR patients (median age, 81.2 years) were significantly older ($P < .001$) than SAVR patients (median age, 67.7 years) and had more baseline comorbid conditions (median Charlson Index, 3 vs 2; $P < .001$), including a higher incidence of a history of atrial fibrillation (43% vs 16%; $P < .001$) and lower ejection fraction (49% vs 53%; $P < .001$). However, TAVR patients received significantly less intraoperative midazolam (median dose, 2.0 mg) than did SAVR patients (median dose, 5.0 mg).

Table 1
Baseline characteristics

Characteristic	Surgical (n = 121)	Transcatheter (n = 105)	P
Age, median; mean (SD), y	67.7; 66.1 (13.5)	81.2; 79.9 (9.5)	<.001
Sex, No. (%) of patients			.28
Female	49 (40)	50 (48)	
Male	72 (60)	55 (52)	
Race, No. (%) of patients			.06
White	109 (91)	103 (98)	
African American	10 (8)	2 (2)	
Not reported	2 (2)	0 (0)	
Charlson Comorbidity Index, median; mean (SD)	2.0; 2.1 (1.8)	3.0; 3.3 (1.8)	<.001
Ejection fraction before procedure, mean (SD), %	53 (12)	49 (12)	<.001
Atrial fibrillation, No. (%) of patients	19 (16)	45 (43)	<.001
Intraoperative midazolam, median; mean (SD)	5.0; 3.9 (2.0)	2.0; 1.9 (1.7)	<.001
Excluded, No. of patients			
Postprocedural death	1	3	
Persistent coma	3	0	

Table 2
Postoperative delirium

Postoperative delirium	Aortic valve replacement, No. (%) of patients	
	Surgical (n = 121)	Transcatheter (n = 105)
Absent	95 (79)	85 (81)
Present	26 (21)	20 (19)

Table 3
Potential risk factors for development of postoperative delirium

Risk factor	Odds ratio	95% CI	P
Age (10-year increments)	1.37	0.97-1.91	.07
Preoperative ejection fraction (5%)	0.96	0.83-1.10	.54
Charlson Comorbidity Index	1.05	0.87-1.27	.61
Midazolam	0.86	0.71-1.05	.15
Procedure (transcatheter vs surgical)	0.40	0.18-0.92	.03

The overall prevalence of postoperative delirium in both groups was 20%, with rates of 19% in the TAVR group and 21% in the SAVR group (Table 2). This small difference in prevalence was not significant ($P = .65$). The identified potential risk factors for postoperative delirium are summarized in Table 3. Increasing age was associated with worsening neurological outcomes: odds ratio, 1.37; 95% CI,
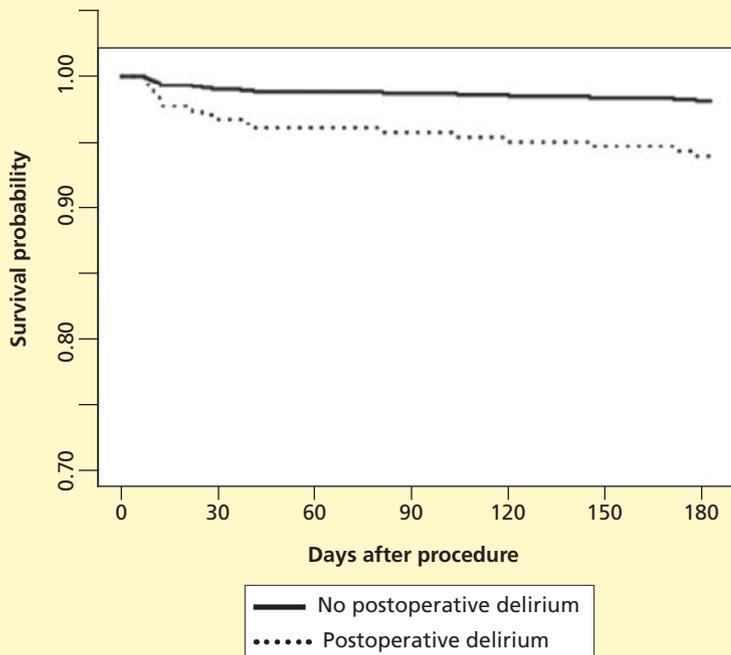
Figure 2 Six-month survival adjusted for age and procedure type.

0.97-1.91; $P = .07$. Odds for delirium were lower in TAVR patients than in SAVR patients (odds ratio, 0.4; 95% CI, 0.18-0.92; $P = .03$), after adjustments for the preidentified risk factors of age, Charlson Comorbidity Index, preoperative ejection fraction, and total intraoperative dose of midazolam.

At 30 days and 6 months, mortality was higher in the TAVR group than in the SAVR patients: 7.6% vs 1.7%, $P = .03$ and 14.3% vs 2.5%, $P = .001$, respectively. Independent of procedure type and age, delirium was associated with a 3-fold higher risk for death by 6 months: hazard ratio, 3.4; 95% CI, 1.3-8.8; $P = .01$ (Figure 2). Incorporating the Charlson Comorbidity Index into the analysis yielded a hazard ratio of 3.4 (95% CI, 1.28-9; $P = .01$).

Discussion

The main finding of this study was that delirium occurred in 1 of 5 patients undergoing an aortic valve replacement. Despite being older and having more comorbid conditions than SAVR patients, TAVR patients had a lower probability of postoperative delirium. Independent of procedure type and age, delirium after aortic valve replacement was associated with a higher mortality at 6 months, after adjustments for potential confounders.

The prevalence of delirium in patients who had aortic valve replacement was lower than the reported rates of delirium in patients treated with mechanical ventilation in medical and surgical ICUs, but similar to rates reported for patients in the CVICU.[6,18] The

difference may be related to the severity of illness, concomitant organ failures and metabolic derangements, sepsis, and ICU management factors such as sleep deprivation and exposure to psychoactive medications, all of which are all more prevalent in medical and surgical ICU patients than in patients in the CVICU because of the longer lengths of stay in the medical and surgical units.

We found that patients undergoing TAVR were less likely than SAVR patients to experience delirium, after accounting for TAVR patients' higher age and number of comorbid conditions. This finding is in line with recent published data, although our delirium rates were much lower than the 29% vs 51% for TAVR and SAVR patients, respectively, reported by Maniar et al.[15] The increased risk for postoperative delirium in SAVR patients compared with TAVR patients may be related to the aortic cross-clamping and cardiopulmonary bypass that are essential elements of the SAVR procedure. These elements and the duration of cardiopulmonary bypass have been associated with increased rates of delirium.[19] Also, the cardiotomy required to perform any valve replacement may cause air to enter the circulation, potentially increasing the risk for cerebral air microemboli and delirium.[20]

Although increasing age was marginally associated with an increased probability of delirium in our study, comorbid conditions, preoperative ejection fraction, and dose of midazolam were not associated with a greater likelihood of delirium in the multivariable modeling. Other investigators[14] found that age, a nontransfemoral approach, current smoking, carotid artery disease, and preoperative atrial fibrillation were risk factors for delirium in TAVR patients. Patients undergoing TAVR are considered inherently at high risk for delirium not only because of their major comorbid conditions but also because of the inherent risks for cerebral embolization of aortic plaques and/or valvular particulate matter associated with TAVR.[21] In the majority of our TAVR patients, a transfemoral approach was used, a characteristic that may explain our lower risk for delirium.

Mortality rates at 30 days and 6 months were significantly higher in the TAVR group than in the SAVR group, although not different from previously reported rates in TAVR patients.[14,22] Compared with SAVR patients, our TAVR patients were older, had more comorbid illnesses, and had higher rates of preoperative atrial fibrillation. This difference in severity of illness most likely accounts for the expected higher rates of postoperative mortality in the TAVR patients. We did not use propensity score matching

of TAVR and SAVR patients because our aim was not to determine the independent role of the surgical procedure on 6-month mortality but rather to assess the effect of postoperative delirium on mortality after aortic valve replacement. Independent of procedure type, age, and comorbid conditions, the presence of delirium led to a 3-fold higher risk for mortality at 6 months in our patients. Interestingly, postoperative delirium reportedly can confer a higher mortality in transfemoral TAVR (39% vs 13%; $P = .003$) but not in nontransfemoral TAVR (33% vs 36%; $P = .84$).[14] Our findings are in line with data on other populations of patients for whom the presence of delirium portends worse clinical outcomes, including increased mortality, longer hospitalizations, and higher rates of complications after procedures.[2,3] This emphasizes the importance of having highly skilled critical care nursing staff monitor for delirium in the postoperative period by using a validated delirium monitoring instrument. Establishing nonpharmacological and pharmacological delirium management algorithms is important to ensure that delirium is addressed in a timely manner when diagnosed. Nonpharmacological interventions can reduce the incidence of delirium in critically and noncritically ill patients.[23,24]

Our study has several limitations. First, the retrospective nature increases the likelihood of confounding by indication. To mitigate this confounding, we adjusted for known confounders (age, comorbid conditions, ejection fraction, and midazolam use) in our analysis, although we acknowledge that our adjustment does not include all possible confounders. Second, we limited the number of confounders we accounted for according to standard recommendations of $N/10$, where N is the number of patients with the event (delirium in this instance), and determined that the model was an appropriate fit: however, our model might have been slightly overfit. Third, we were unable to study nonlinear associations or to determine if specific interactions occurred between our covariates because of our limited number of patients with delirium and our concern for overfitting our models. As in any observational study, additional unknown confounders might have had an effect on the associations we observed. Finally, the low rates of delirium and mortality in our sample allowed us to examine only a limited subset of risk factors that we hypothesized would be important. Thus, the association between mortality and delirium may be confounded by unmeasured variables. Last, the incidence of delirium in our patients might be underreported; no confirmatory evaluation was performed after the original determination of delirium was made by using the RASS and CAM-ICU scoring systems. Despite some of these limitations, we think our study supports recently published data as outlined above on the incidence of delirium in patients undergoing SAVR and TAVR and the effect of delirium on mortality. Importantly, our study builds on earlier studies, because we assessed patients' risk factors and outcomes of delirium by accounting for other confounders, and highlights the need to monitor for delirium in patients having aortic valve replacement because of the high risk for mortality associated with delirium.

Conclusions

Delirium is a common finding in patients after aortic valve replacement. We found that compared with SAVR patients, TAVR patients have a lower probability for delirium, after adjustments for age, comorbid conditions, preoperative ejection fraction, and dose of midazolam during surgery. Delirium in both SAVR and TAVR groups portended a 3-fold higher risk for mortality at 30 days and 6 months, supporting the notion that monitoring for delirium should be the standard of care for all patients who have aortic valve replacement. More prospective studies are needed to further characterize the incidence, risk factors, and consequences of delirium in patients undergoing TAVR. Reducing the incidence of delirium represents an important opportunity to improve outcomes for patients who have SAVR or TAVR.

Delirium occurred in 1 of 5 patients undergoing aortic valve replacement.

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