Silent cerebral ischemia detected by magnetic resonance imaging can predict postoperative delirium after total arch replacement for aneurysm

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ABSTRACT

Objective: To identify whether preoperative magnetic resonance imaging findings of the brain can predict postoperative delirium in patients who undergo arch replacement for aneurysms.

Methods: Overall, 193 patients who underwent aortic replacement for the first time at a single institution between April 2014 and September 2020 were enrolled in this retrospective study. After we excluded patients with acute aortic dissection, no preoperative magnetic resonance imaging findings of the brain, and postoperative cerebral infarction, 50 patients were included and divided into 2 groups, according to their confusion scale results: postoperative delirium (group D) and nonpostoperative delirium (group ND). Preoperative magnetic resonance imaging findings of the brain were classified into lacunar stroke, periventricular hyperintensity, and deep subcortical white matter hyperintensity groups; the latter 2 groups were further classified based on the Fazekas scale, grade 0 to 3.

Results: There were 23 patients (46%) in group D and 27 (54%) in group ND. The mean age was significantly greater in group D than in group ND (75 vs 70 years; \( P = .007 \)). The mean operative time was significantly longer in group D than in group ND (447 vs 384 minutes; \( P = .024 \)). As for preoperative magnetic resonance imaging findings of the brain, there were significantly more lacunar stroke cases in group D than in group ND (\( P = .027 \)). In multivariable logistic regression with stepwise selection, high-grade periventricular hyperintensity was significantly related to postoperative delirium (odds ratio, 9.38; 95% confidence interval, 1.55-56.56; \( P = .015 \)).

Conclusions: Silent cerebral ischemia detected by preoperative magnetic resonance imaging of the brain was a significant risk factor for postoperative delirium. (JTCVS Open 2022;10:87-96)
to be associated with increased mortality and morbidity, prolonged hospital stays, and increased hospitalization costs.\textsuperscript{1,2,3,4} Krzych and colleagues\textsuperscript{5} reported that, overall, the 30-day mortality for patients with PD after cardiac surgery was 15.2\%. Especially in patients with aortic aneurysms (AAAs), total arch replacement (TAR) has a high risk of resulting in neurologic complications, including PD.\textsuperscript{11,12} However, the relationship between preoperative MRI findings of the brain due to previous pacemaker implantation (n = 2), and those who had postoperative cerebral infarction (n = 7) were excluded. The remaining 50 patients with AAAs were included and divided into 2 groups: postoperative delirium (group D) and nonpostoperative delirium (group ND) groups. During the preoperative interview of patients and their families, it was confirmed that all patients had no history of stroke or other neurologic diseases, including previous transient ischemic attack, history of seizure/neurologic trauma/falls, or history of psychiatric/neurologic disorders (depression, Alzheimer disease, and Parkinson disease). Moreover, it was also confirmed that no patient in the present study was taking benzodiazepines, antidepressants, or other psychotropic medications.

\textbf{METHODS}

\textbf{Ethical Approvals}

This study was approved by the ethics committees of our hospital on April 20, 2021 (approval number: 19207). Given the retrospective, observational nature of the study design, the Ethics Committee waived the requirement of informed consent.

\textbf{Patients and Study Design}

Between April 2014 and September 2020, a total of 193 patients underwent TAR or hemiarch replacement for the first time at a single institution (Figure 1). Patients with acute aortic dissection (n = 134), those with no preoperative MRI of the brain, the aortic root, and those who had postoperative cerebral infarction (n = 7) were excluded. The remaining 50 patients with AAAs were included and divided into 2 groups: postoperative delirium (group D) and nonpostoperative delirium (group ND) groups. During the preoperative interview of patients and their families, it was confirmed that all patients had no history of stroke or other neurologic diseases, including previous transient ischemic attack, history of seizure/neurologic trauma/falls, or history of psychiatric/neurologic disorders (depression, Alzheimer disease, and Parkinson disease). Moreover, it was also confirmed that no patient in the present study was taking benzodiazepines, antidepressants, or other psychotropic medications.

\textbf{Surgical Techniques}

Our institutional standard anesthetic management was used for all patients. The surgical technique demonstrating TAR is shown in Video 1. Forty-six patients underwent TAR, and 4 patients underwent hemiarch replacement, through a median sternotomy. An 8-mm graft was initially anastomosed to the left axillary artery connected to the SCP circuit. The ascending aorta was crossclamped, and cardioplegic arrest was induced. The proximal anastomosis was made at the level of the sinotubular junction. When the rectal temperature was less than 26° C, hypothermic circulatory arrest was started along with retrograde cerebral perfusion. After selective cerebral perfusion (SCP) canulas had been inserted into the brachiocephalic artery and into the left carotid artery, and the graft had been anastomosed to the left axillary artery connected to the SCP circuit, retrograde cerebral perfusion was stopped, and SCP was initiated. The blood flow in the carotid arteries was monitored using echocardiography during SCP. The distal anastomosis was performed at zone 1 or 2 using a frozen elephant trunk device. After completion of the distal anastomosis, systemic perfusion was restarted, and the patient was rewarmed. Two grafts were anastomosed in an end-to-end fashion, and the aorta was declamped. Thereafter, the supra-aortic vessels were individually anastomosed to the 4-branched arch prosthesis.

\textbf{Intraoperatively}, the mean arterial pressure was maintained above 60 mm Hg using catecholamines and blood transfusions. Cardiopulmonary bypass flow was controlled with a goal of a cardiac index of 2.4 or greater. In addition, blood transfusions were used to maintain the hemoglobin level above 8.0 g/dL. As for intraoperative neurological monitoring, cerebral oximetry was used.

\textbf{Management of Delirium}

In our institution, dexmedetomidine was administered to patients with PD during their stay in the intensive care unit (ICU). In addition, if patients with PD were able to take medications, we prescribed ramelteon instead of benzodiazepines because they have better efficacy.

\textbf{Image Assessment}

At our institution, most MRIs of the brain were performed less than 1 month before surgery using a 1.5-T or 3.0-T conventional clinical scanner. Standard anatomical imaging of the brain included axial T1, axial

\begin{table}[h]
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\textbf{Abbreviations and Acronyms} & \\
\hline
\textbf{AAA} & aortic arch aneurysm \\
\textbf{AR} & arch replacement \\
\textbf{CI} & confidence interval \\
\textbf{DSWMH} & deep subcortical white matter hyperintensities \\
\textbf{ICDSC} & Intensive Care Delirium Screening Checklist \\
\textbf{ICU} & intensive care unit \\
\textbf{MRI} & magnetic resonance imaging \\
\textbf{NCS} & Neelon and Champagne confusion scale \\
\textbf{NPD} & nonpostoperative delirium \\
\textbf{OR} & odds ratio \\
\textbf{PD} & postoperative delirium \\
\textbf{PVH} & periventricular hyperintensity \\
\textbf{SCP} & selective cerebral perfusion \\
\textbf{TAR} & total arch replacement \\
\textbf{TEVAR} & thoracic endovascular aortic repair \\
\textbf{WMH} & white matter hyperintensity \\
\hline
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\end{table}
T2, axial diffusion, axial T2 fluid-attenuated inversion recovery, and angiography. MRI findings of the brain were evaluated by a study-blinded neurologist at our institute, who classified the results into 3 groups: lacunar stroke, periventricular hyperintensity (PVH), and DSWMH. The levels of PVH and DSWMH were classified according to the Fazekas score, with a 4-point scale. Images from Fazekas 0 to 3 scale are shown in Figure 2. Because grade 2 or 3 on the Fazekas scale indicates an extensive amount of white matter lesions, patients with grade 2 or 3 on the Fazekas scale were identified as having high-grade PVH or high-grade DSWMH.

PD Assessment

All patients were evaluated for confusion using the Neelon and Champagne confusion scale (NCS) or the Intensive Care Delirium Screening Checklist (ICDSC) by the nurses while the patients were in the ICU. The NCS is based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and the Delphi panel, and it contains 3 subscales: processing, behavior, and physiological status. All subscales include 3 questions. Overall, the scores range from 0 to 30: 0 to 19, acute to moderate confusion; 20 to 24, mild confusion; 25 to 26, risk of confusion; and 27 to 30, normal status. In this study, a score of ≤24 points fulfilled the criteria for delirium on the NCS. In contrast, the ICDSC consists of 8 items based on the criteria and features of delirium included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: impaired consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance, and symptom fluctuation. A score of ≥4 points fulfilled the criteria for delirium on the ICDSC. At our institution, assessment using the ICDSC began in April 2018. Therefore, up until March 2018, patients were evaluated using the NCS; thereafter, patients were evaluated using the ICDSC.

Statistical Analysis

All analyses were performed using SPSS statistics software, version 23.0 (IBM Corp). Continuous variables are presented as mean with standard deviation, and categorical variables are presented as numbers or percentages. Comparisons between the groups (group D vs group ND) were performed using the t-test or Mann–Whitney U test for continuous variables and the Fisher exact test for categorical variables, as appropriate. There were no missing values in the data. The correlation analysis in group D was performed using the Spearman rank correlation test to assess the relationship between the length of PD and the Fazekas scale of PVH. Spearman coefficients were denoted by \( r_s \). A multivariate forced entry logistic regression analysis was performed to determine the risk factors. This analysis included age, chronic kidney disease, mechanical ventilation time, circulatory arrest time, and PVH. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable.

RESULTS

Preoperative Characteristics

Preoperative and postoperative characteristics are shown in Table 1. A total of 50 patients were included. The mean age of patients was 73.0 ± 7.0 years, and 38 (76%) were male. Overall, 23 (46%) patients developed delirium. Patients in group D were significantly older than those in group ND (75.0 ± 6.7 years vs 73.0 ± 7.0 years).
70.0 ± 7.0 years; \( P = .007 \)). There were no significant differences between the groups in terms of sex or common comorbid conditions.

**Operative and Postoperative Characteristics**

Perioperative and postoperative characteristics are shown in Table 1. The proportion of patients who underwent TAR did not differ between the groups. The mean operative time was significantly longer in group D than in group ND (447 minutes vs 384 minutes; \( P = .024 \)). The mean circulatory arrest time was also significantly longer in group D than in group ND (51 minutes vs 42 minutes; \( P = .039 \)). There was no significant difference in the ICU length of stay between the 2 groups. The mean cerebral oximetry value before and after the circulatory arrest showed a significant difference. However, there was no significant difference in the cerebral oximetry value between the 2 groups. Regarding other parameters, no significant differences were observed between the 2 groups.

**MRI Findings**

The relationship between preoperative MRI findings and PD is shown in Table 2. There were significantly more lacunar strokes in group D than in group ND (62% vs 10%; \( P = .027 \)) (Figure 3, A, Figure 4). Patients with high-grade PVH had significantly more delirium than those without (group D vs group ND; \( P < .01 \)) (Figure 3, B, Figure 4). In addition, patients with high-grade DSWMH had significantly more delirium than those without (group D vs group ND; \( P < .042 \)) (Figure 3, C, Figure 4).
Correlation Analysis Between the Fazekas Scale of PVH and the Length of PD

In group D (n = 23), the relationship between the Fazekas scale of PVH and the length of PD is shown in Figure 5. There was no significant correlation between the grade of PVH and the length of PD (rs = 0.065, n = 23, P = .767).

Multivariate Regression Analysis

Results of the multivariate regression analysis are presented in Table 3, and age, chronic kidney disease, mechanical ventilation time, circulatory arrest time, and PVH are included. The multivariate regression analysis identified a total of 2 independent parameters that were associated with PD: high-grade PVH (OR, 9.38; 95% CI, 1.55-56.56; P = .015) and circulatory arrest time (OR, 1.06; 95% CI, 1.00-1.13; P = .044).

DISCUSSION

The results of this retrospective study suggested that high-grade PVH could independently predict PD after AR for AAAs. In addition, patients with PD tended to have radiographic evidence of lacunar infarcts and high-grade DSWMH. We also identified circulatory arrest time as a predictor of PD in patients after AR.
Various factors can be used to predict PD after cardiac surgery. Järvelä and colleagues reported that the duration of mechanical ventilation time was associated with PD after cardiac surgery. Morandi and colleagues suggested a relationship between statins and PD in cardiac surgery. In the present study, both mechanical ventilation time and statins did not predict PD in patients after AR.

Previous studies suggested that WMH and cerebral infarcts can also predict PD after surgery. Kant and colleagues reported that WMH is significantly associated with adverse postoperative neurologic outcomes in patients who have undergone TAR. In consensus with the study by Kant and colleagues, this study clarified that WMH was related to PD after cardiac surgery, especially AR. However, we found lacunar infarcts to be associated with PD, although the studies by Kant and colleagues and Ikeno and colleagues did not show an association between lacunar infarcts and PD.

According to the reports by Fong and colleagues neuroanatomical localization of delirium pathology has implications for understanding both symptoms and underlying mechanisms. For example, attention is associated with the bifrontal areas, thalamus, and pons. Cognition is associated with the frontal and temporal regions. Breteler and colleagues showed a relationship between WMH and impairment of the subcorticofrontal functions that are associated with attention. Particularly, in patients with delirium, frontal cerebral blood perfusion abnormalities have been reported. Moreover, several studies have reported that WMH is associated with mild disordered cognition. The present study also suggested that patients with

### TABLE 2. Findings from the preoperative magnetic resonance imaging of the brain

|                          | Total (n = 50) | PD (n = 23) | NPD (n = 27) | P value |
|--------------------------|---------------|-------------|--------------|---------|
| Lacunar infarcts, %      |               |             |              |         |
|                          | 26 (52)       | 16 (70)     | 10 (37)      | .027    |
| Fazekas scale PVH, grade |               |             |              |         |
| mean ± SD                | 1.78 ± 0.92   | 2.22 ± 0.78 | 1.40 ± 0.87  | <.01    |
| 0                        | 4 (8)         | 1 (4)       | 3 (11)       |         |
| 1                        | 16 (32)       | 2 (9)       | 14 (52)      |         |
| 2                        | 17 (34)       | 11 (48)     | 6 (22)       |         |
| 3                        | 13 (26)       | 9 (39)      | 4 (15)       |         |
| High-grade               | 30 (60)       | 20 (87)     | 10 (37)      | .001    |
| DSWMH, grade, mean ± SD  | 2.00 ± 0.93   | 2.26 ± 0.90 | 1.56 ± 0.83  | <.01    |
| 0                        | 3 (6)         | 1 (4)       | 2 (7)        |         |
| 1                        | 16 (32)       | 4 (18)      | 12 (44)      |         |
| 2                        | 15 (10)       | 6 (26)      | 9 (33)       |         |
| 3                        | 16 (32)       | 12 (52)     | 4 (15)       |         |
| High-grade               | 31 (62)       | 18 (78)     | 13 (48)      | .042    |

The mean (SD) or median (IQR) is presented for continuous data or non-normally distributed data, respectively, and n (%) for categorical data. The t-test was performed on continuous data, and the Mann–Whitney U test was performed for non-normally distributed data. The P value indicates the difference between the D and ND groups. Patients with grade 2 or 3 on the Fazekas scale were identified as having high-grade PVH or high-grade DSWMH. PD, Postoperative delirium; ND, nonpostoperative delirium; PVH, periventricular hyperintensity; SD, standard deviation; DSWMH, deep subcortical white matter hyperintensity; IQR, interquartile range.

![FIGURE 3. The proportion of brain magnetic resonance imaging findings in groups D and ND. There were significantly more lacunar infarcts (A), high-grade PVH (B), and high-grade DSWMH (C) in group D than in group ND. D, Postoperative delirium group; ND, nonpostoperative delirium group; PVH, periventricular hyperintensity; DSWMH, deep subcortical white matter hyperintensity.](image-url)
Silent cerebral ischemia detected by MRI can predict postoperative delirium after total arch replacement

Total arch replacement (first time) n = 193

Total arch replacement for thoracic aneurysm n = 59

Postoperative delirium (Group D) n = 23

Non-postoperative delirium (Group ND) n = 27

Assessment of postoperative delirium
NEECHAM confusion scale
ICDSC

Preoperative MRI findings
lacuna infarction
PVH
DSWH

Implications
➢ Silent cerebral ischemia was risk factor for PD.
➢ Brain MRI as a tool in thoracic aortic surgery
  • patient selection
  • operator selection
  • therapy selection

FIGURE 4. Summary of this study. We analyzed whether preoperative MRI findings of the brain can predict postoperative delirium in patients undergoing total arch replacement for aneurysms. MRI, Magnetic resonance imaging; D, postoperative delirium group; ND, nonpostoperative delirium group; NEECHAM, Neelon and Champagne; ICDSC, Intensive Care Delirium Screening Checklist; PVH, periventricular hyperintensity; DSWMH, deep subcortical white matter hyperintensities; PD, postoperative delirium.

High-grade PVH or DSWMH, which indicates severe WMH, were more at risk of developing PD.

Lacunar infarcts commonly occur in the thalamus, pons, and basal ganglia, and these abnormalities can cause inattention. Although lacunar infarcts were not an independent predictor of PD, patients with delirium in this study often had evidence of these lesions. Therefore, the results of this study might support a relationship between the presence of lacunar infarcts and PD.

There have been some reports stating that WMH and lacunar infarcts might be associated with strokes. Bokura and colleagues suggested that WMH and silent lacunar infarcts can be important stroke risk factors and might be associated with increased mortality rates. Moreover, Ikeno and colleagues reported that WMH was associated with adverse postoperative events after AR. Thus, the preoperative MRI assessment of the brain appeared to be important, especially in high-risk patients undergoing AR. In the present study, patients suffering from postoperative stroke were excluded because the focus of the study was the relationship between preoperative MRI findings and PD, and thus, the adverse outcomes did not differ between the 2 groups. However, the present study suggested that WMH...
could influence not only the hard outcomes, eg, mortality and/or stroke, but also the secondary outcome, ie, PD after AR.

Whether preoperative MRI findings are associated with the length of PD is an interesting issue. In this study, the length of PD was not related to the PVH grade. However, the analysis was performed in group D, which was small in size. The relationship between delirium severity and PVH grade should be clarified in further studies.

The risk factors for PD are classified into 2 categories: predisposing and precipitating factors.26 In patients with AAAs, predisposing factors that increase the risk of PD include advanced age and atherosclerotic aneurysms.4,27 The present study suggested that high-grade PVH was a predisposing factor. Although age, lacunar infarcts, and DSWMH were not independent predictors of PD, our univariate regression analysis found that patients with delirium tended to be older and have the presence of lacunar infarcts.

Thus, advanced age, lacunar infarction, and DSWMH could also be predisposing factors. In contrast, precipitating factors can also result in the development of PD, and it is widely known that hypothermic circulatory arrest is associated with PD.5,28 We also identified circulatory arrest time as a precipitating factor for PD.

Importantly, the prediction of PD using predisposing factors can help clinicians in their decision-making regarding (1) patient selection, (2) operator selection, and (3) therapy selection.

Patient Selection

To date, we have not rejected any patient for conventional open AR because of MRI findings of the brain. Based on the findings of the present study, however, it would be a reasonable option to exclude certain patients with an extremely high risk of PD from conventional open AR surgery.

Operator Selection

The present study demonstrated that circulatory arrest time was a risk factor for PD. To shorten the circulatory arrest time and minimize the risk of PD, an experienced surgeon should be selected for patients predicted to have a very high likelihood of developing PD. Indeed, in the present study, AR was performed by several operators, which might have resulted in increased operation and circulatory arrest times in group D compared with group ND. Operator factors can influence the surgical time, as we have previously reported.29 Surgical education is important, but considering the results of the present study, an experienced operator should perform AR in high-risk patients.

Therapy Selection

In the contemporary era of developing endovascular treatments, thoracic endovascular aortic repair (TEVAR) is a reasonable alternative for patients with AAA. If a patient was at extremely high risk for developing PD with anatomy unsuitable for TEVAR, then this patient should not be considered for AR. However, many patients with AAA can be treated with both open conventional AR and debranching TEVAR. In certain high-risk patients, TEVAR can be selected to minimize the risk of PD based on the preoperative MRI findings.

At our institution, MRI of the brain is performed as a routine preoperative evaluation for cardiac surgery, as is the practice in most Japanese institutions. However, such liberal usage of expensive MRIs of the brain might not be currently accepted in other countries or in Japan in the future. Nevertheless, the results of the present study indicate that prediction of PD by preoperative MRI of the brain benefits certain patient groups, such as older individuals.

Appropriate delirium management is also important to minimize the complications of PD. In our institution, we administered dexmedetomidine to patients during their

| TABLE 3. Multivariate analysis of risk factors for postoperative delirium |
|-----------------|-------|----------|--------|
| Risk factor                  | OR    | 95% CI   | P value |
| Age (per 1-year increase)   | 1.08  | 0.96-1.22| .187   |
| CKD                         | 3.62  | 0.28-47.73| .328   |
| Mechanical ventilation time (per 1-hour increase) | 1.04  | 0.98-1.08| .304   |
| Circulatory arrest time (per 1-minute increase) | 1.06  | 1.00-1.13| .044   |
| PVH                         | 9.38  | 1.55-56.56| .015   |

A multivariate simultaneous forced entry logistic regression analysis was performed. Age, CKD, mechanical ventilation time, circulatory arrest time, and PVH were included. OR, Odds ratio; CI, confidence interval; CKD, chronic kidney disease; PVH, periventricular hyperintensity.
stays in ICU. Djaiani and colleagues suggested that dexmedetomidine reduced the incidence, delayed the onset, and shortened the duration of PD in elderly patients after cardiac surgery. We also prescribed ramelteon instead of benzodiazepines because of its better efficacy. In addition, we allowed the patients’ families to visit the patients. Mailhot and colleagues suggested the efficacy of interventions involving the patient’s family.

This study has several limitations. First, the sample size was small, thereby reducing the study’s statistical power. Probably for this reason, well-known risk factors for PD (ie, length of ICU stay and ventilation time) did not reach statistical significance in the present study. Second, this was a retrospective, single-center study. Third, the screening tools used to detect PD varied at different study periods. Although NCS and ICDSC are appropriate delirium screening tools, there have been no reports validating these 2 delirium screening tools in the ICU simultaneously. In addition, the ICDSC assesses the severity of delirium, but not all patients were assessed with the ICDSC. The NCS might assess conditions other than delirium because it includes the subscale of physiological status. Therefore, the measurement of delirium severity may not have been consistent between the 2 groups. Nevertheless, we believe that our study is a worthwhile investigation of the relationship between preoperative MRI findings and PD because PD was assessed prospectively by nursing staff routinely without prejudice. Fourth, some patients could have had mild cognitive decline. All the patients and their families were carefully interviewed regarding dementia because dementia is one of the contraindications for AR in our institute; it was confirmed that no patient had preoperative symptomatic cognitive dysfunction. However, the lack of a preoperative test for cognitive function is a strong limitation of the present study. Some patients thought to have no cognitive dysfunction may have had deficits that were too subtle to be detected despite our screening methodology. Fifth, long-term follow-up data regarding PD were not available due to the retrospective nature of our study. Finally, the 7 patients who suffered from obvious postoperative stroke were excluded from the analysis because the main focus of the present study was PD in patients without symptomatic stroke. However, the relationship between preoperative cerebral ischemia and postoperative stroke should be investigated in further studies.

CONCLUSIONS

PVH detected by MRI and prolonged circulatory arrest time can predict PD after AR for an AAA. This study showed the potential of MRI of the brain as a tool for selection of patients, operative methods, and operators for the treatment of AR in patients with a significant risk of PD. However, further studies with larger sample sizes are required.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** postoperative delirium, magnetic resonance imaging, white matter intensity, total arch replacement