Supplementary information

Cerebral ischemic injury after transcatheter aortic valve replacement in patients with pure aortic regurgitation

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Materials and methods

A total of 352 consecutive patients who underwent self-expanding TAVR with available DW-MRI images between July 2018 to June 2021 were enrolled from the Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population (TORCH) registry (NCT02803294), which is an ongoing single-center prospective cohort study designed to evaluate the safety and effectiveness of TAVR in patients with severe AS or AR in China. The AS group included patients with severe aortic valve stenosis, whereas the pure AR group comprised patients with aortic jet peak velocity on continuous-wave Doppler of ≤2.5 m/s. All adverse clinical events were reviewed by the clinical event committee. Major Adverse Cardiovascular Events (MACEs) were defined as the composite of death, myocardial infarction, and stroke. Stage 4 or 5 chronic kidney disease (CKD 4/5) was defined as estimated glomerular filtrate rate (eGFR) of less than 30 mL/min per 1.73 m².

Exclusions were made as follows: (1) unavailable DW-MRI examination for various reasons, such as in-hospital death, conversion to open-heart surgery, intolerable physical condition, claustrophobia, contraindications for MRI, and refusal of the DW-MRI examination; (2) DW-MRI results with poor-quality imaging or beyond the window period; (3) prior stroke or transient ischemic attack within three months; (4) prior aortic valve replacement; (5) non-self-expanding transcatheter valve implantation. All enrolled patients completed a 30-d follow-up.

Patients were routinely screened for TAVR based on transthoracic echocardiography and multi-detector computed tomography (MDCT). The multidisciplinary heart valve team assessed aortic root anatomy and then formulated detailed procedural strategies using 3mensio Workstation (3mensio Medical Imaging BV, Bilthoven, the Netherlands). Hangzhou Solution was used as a prosthesis sizing selection guide in bicuspid AS patients. The landing zone calcium grading was consistent with an expert consensus document of the Society of Cardiovascular Computed Tomography (CT). The calcium volume score at the aortic root was measured from 5 mm below the annulus plane to the sinotubular junction plane at the threshold of 650 Hounsfield units (HU),

850 HU, and HU+100 (John et al., 2010).

All TAVR procedures were performed in the hybrid operating room under intravenous anesthesia or local anesthesia with sedation. Other procedure-related details were as mentioned previously (Fan et al., 2020). Intravenous unfractionated heparin was used to target activated clotting time between 250 and 300 s intraoperatively. Different self-expanding valves were implanted, such as the CoreValve/Evolut R (Mezzzdtronic, Minneapolis, MN, USA), VenusA-Valve (Venus Medtech, Hangzhou, China), VitaFlow (Microport, Shanghai, China), and Taurus One-Valve (Peijia Medical, Suzhou, China) by transfemoral (TF) access, and J-Valve (Suzhou Jiecheng Medical Technology Co., Ltd.) by transapical (TA) access. The loading dose of dual-antiplatelet therapy (acetylsalicylic acid and clopidogrel) was not mandatory before the procedure. After the procedure, the anticoagulation regimens were chosen for patients with anticoagulation indications, whereas single antiplatelet regimens were continued for life after three to six months of the dual-antiplatelet regimen for patients without anticoagulation indications.

Cerebral DW-MRI was scanned mainly with a 1.5-T or 3.0-T scanner (GE Signa, GE Healthcare, Milwaukee, Wisconsin, USA) post-procedure within the window period. The regular imaging scheme involved transversal T2-weighted turbo spin echo (1.5-T: repetition time/echo time=4800 ms/100 ms; 3.0-T: repetition time/echo time=3300 ms/80 ms) and transversal fluid-attenuated inversion recovery (1.5-T: repetition time/echo time=6000 ms/120 ms; 3.0-T: repetition time/echo time=1200 ms/140 ms) initially. DW-MRI was performed using a spin-echo echo-planar pulse sequence with diffusion sensitization *b*-values of 0 and 1000 s/mm². For 1.5-T, images were acquired with repetition time/echo time of 2921 ms/78 ms, matrix of 128×256, and total acquisition time of 21.4 s. For 3.0-T, images were obtained with repetition time/echo time of 3866 ms/47 ms, matrix of 128×256, and total acquisition time of 46.3 s. A section thickness of 5 mm and a gap of 1 mm were required. DW-MRI is the most sensitive sequence in detecting acute cerebral infarction, which is presented as hyperintensity on DW-MRI images and as hypointensity on the apparent diffusion coefficient maps.

The described images above after the procedure were regarded as procedural-related cerebral ischemic lesions. MRI images were reviewed by two well-trained physicians blinded to the patients' clinical characteristics and confirmed by neuroradiologists. The detailed MRI analysis protocols and definition of vascular territories were consistent with our previous research (Fan et al., 2020, 2021). The location of cerebral ischemic lesions was determined on the basis of the area of cerebral vascular perfusion, including anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA). Vascular boundary regions were defined as the areas between ACA and MCA (ACA/MCA), MCA and PCA (MCA/PCA), vertebral artery and basilar artery (VA/BA) (Doerner et al., 2018). The number, volume, and location of all cerebral lesions were recorded.

All statistical analyses were performed using IBM SPSS software Version 25.0 (IBM, Armonk, NY, USA). The normality tests of variables were checked primarily using the Shapiro-Wilk test. Continuous data were described as mean±standard deviation (SD) or median (interquartile range (IQR)) and were compared using the Student's *t*-test or Mann-Whitney tests as

appropriate. Categorical data were presented as frequencies (percentages) and compared using Pearson's Chi-square or Fisher's exact test. Variables with a *P* value of <0.10 in the univariate regression models were selected in the multivariate Poisson regression model to determine the correlates of baseline variables with the number of ischemic lesions. The null hypothesis would be rejected for a two-sided value of $P<0.05$. All figures were configured by GraphPad Prism Version 9.0 (GraphPad Software, San Diego, CA, USA).

References

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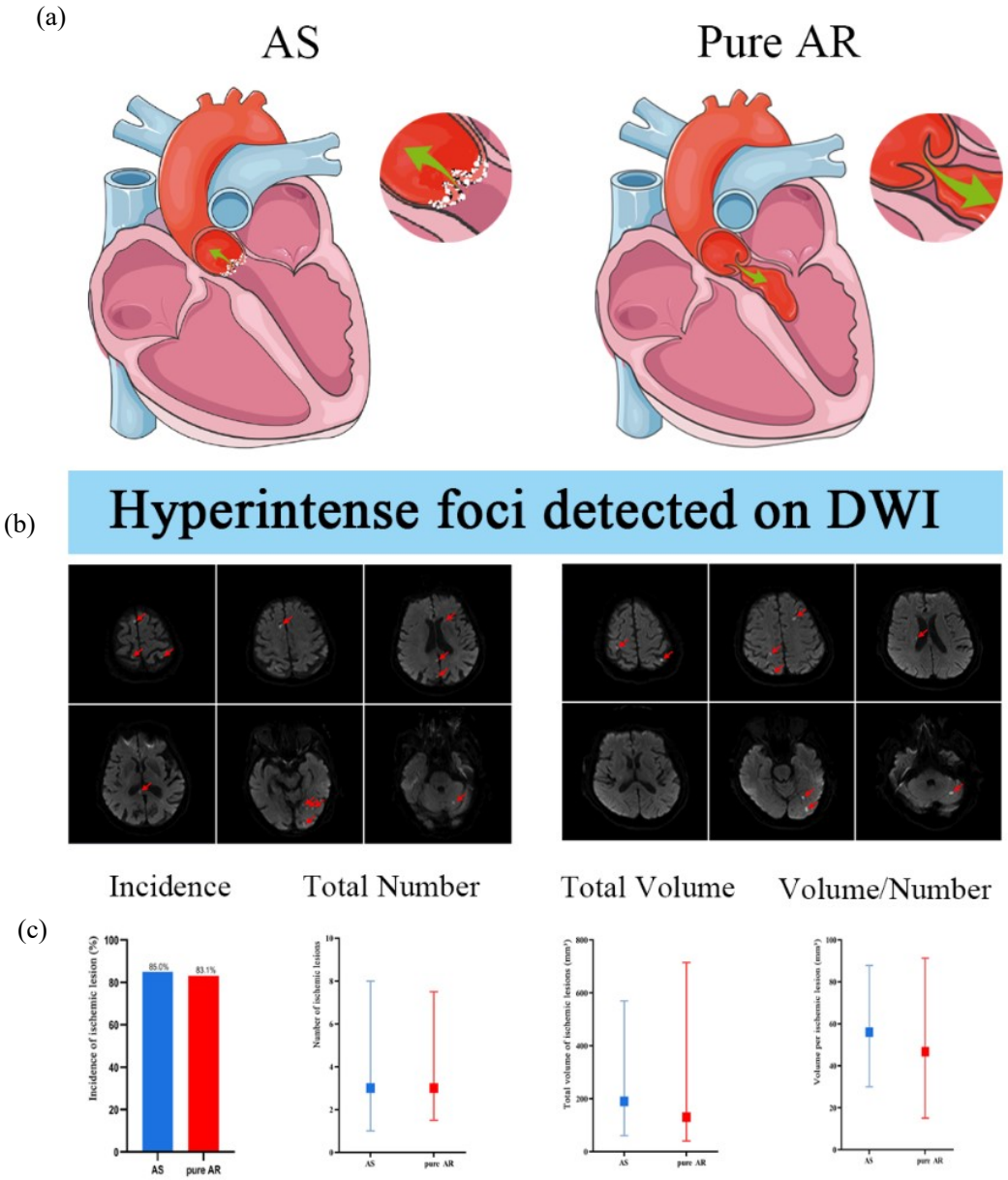

Fig. S1 Comparison of cerebral ischemic lesions by DW-MRI between AS and pure AR patients after TAVR. (a) Schematic diagram of calcific AS and pure AR morphology. (b) DW-MRI obtained in an AS patient and pure AR patient, demonstrating multiple, bilateral ischemic lesions without any apparent neurological symptoms following TAVI (red arrows). (c) Four images showing the incidence of ischemic lesions, number of ischemic lesions, total volume of ischemic lesions, and volume per ischemic lesion in DW-MRI. All values (except incidence of ischemic lesions) are presented as median (IQR). DW-MRI: diffusion-weighted magnetic resonance imaging; AS: aortic stenosis; AR: aortic regurgitation; TAVR: transcatheter aortic valve replacement; TAVI: transcatheter aortic valve implantation; IQR: interquartile range.

Table S1 DW-MRI findings for pure AR patients

Characteristics	Global (*n*=65)	TA (*n*=42)	TF (*n*=23)	*P* value
Patients with new lesions	54 (83.1%)	34 (81.0%)	20 (87.0%)	0.786
Total new lesions	363	235	128	
New lesions per patients	3.0 (1.5–7.5)	3.5 (1.0–8.3)	3.0 (2.0–7.0)	0.923
Patients with a single lesion	5 (9.3%)	4 (11.8%)	1 (5.0%)	0.640
Patients with multiple lesions	49 (90.7%)	30 (88.2%)	19 (95.0%)	
Patients with bi-hemisphere lesions	34 (52.3%)	22 (52.4%)	12 (52.2%)	0.987
Lesion location				
ACA	30 (8.3%)	19 (8.1%)	11 (8.6%)	0.866
ACA/MCA	67 (18.5%)	50 (21.3%)	17 (13.3%)	0.061
MCA	103 (28.4%)	57 (24.3%)	46 (35.9%)	0.018
MCA/PCA	18 (5.0%)	18 (7.7%)	0	0.001
PCA	89 (24.5%)	54 (23.0%)	35 (27.3%)	0.356
VA/BA	56 (15.4%)	37 (15.7%)	19 (14.8%)	0.820
Lesion volume (mm^3)	46.7 (15.0–91.3)	47.3 (14.6–90.6)	45.0 (25.0–109.0)	0.645
Maximal lesion volume per patient (mm^3),	70.0 (20.0–185.0)	70.0 (20.0–177.5)	80.0 (30.0–220.0)	0.804
Total lesion volume per patient (mm^3)	130.0 (40.0–715.0)	135.0 (35.0–745.0)	120.0 (50.0–650.0)	0.837
Patients with total lesion volume of ≥500 mm^3	18 (27.7%)	12 (28.6%)	6 (26.1%)	0.831

All data are presented by number (percentage), number, or median (IQR) for skewed variables. DW-MRI: diffusion-weighted magnetic resonance imaging; AR: aortic regurgitation; TF: transfemoral; TA: transapical; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VA: vertebral artery; BA: basilar artery; IQR: interquartile range.