Supplementary material S1 - Cerebral MRI acquisition and analysis

Cerebral MRI scans were obtained at baseline (within 24 hours prior to TAVI) and at 3 months follow-up. Patients were instructed not to have any caffeinated drinks during the 12 hours prior to MRI. Participants were all, both during baseline and at follow-up, scanned on the same 3-Tesla Philips Ingenia MRI-scanner (Best, the Netherlands) equipped with a 16-channel DStream Head-Spine coil. Foam padding was applied to restrict head motion. The pseudo-continuous ASL (PCASL) sequence was performed with a gradient-echo single-shot echo-planar imaging readout with the following parameters: matrix size = 80x80, voxel-size = 3 x 3 mm, 17 axial slices with 6 mm thickness without a slice-gap, echo time/repetition time = 14.3/4450 ms, SENSE = 2.5, initial post-label delay (PLD) = 2000 ms; slice readout time = 40.6 ms; resulting PLD range for 17 slices = 2000-2650 ms, labeling duration = 1800 ms and two background suppression pulses played at 1850 and 3375 ms after a pre-labeling saturation pulse. 32 control-label pairs were acquired for each scan, for a total scan duration of 4:44 min. The labeling plane was positioned parallel and 90 mm inferior to the center of the imaging volume (the anterior-commissure - posterior-commissure line). A 1x1x1 mm 3D T1-weighted (T1w) scan was included in the imaging protocol for segmentation and registration purposes.

The scan quality was visually reviewed by an experienced neuroradiologist. Next, a region-of-interest segmentation method and arterial spin labelling (ASL) quantification method was applied (1-3). The region of interest segmentation uses grey matter and white matter segmentation (4) and multi-atlas registration of 30 atlases with 83 structural brain regions based on the T1-weighted scans (5, 6). For the temporal lobe and occipital lobe, only the superior parts could be used in the analysis as the inferior parts were excluded from the field-of-view of the ASL scan. Consequently, analysis of the occipital lobe was restricted to the cuneus, and the temporal lobe. Moreover, the temporal lobe was totally excluded from the analysis. Quantification of the raw ASL data into cerebral blood flow included motion-correction (7) or the raw ASL data and partial volume correction (8). This pipeline resulted in the average cerebral blood flow (mL/100g/min) in the grey matter region and of the entire grey matter. The primary outcome was the relative increase (Δ%) in cerebral blood flow per patient from baseline to follow-up.

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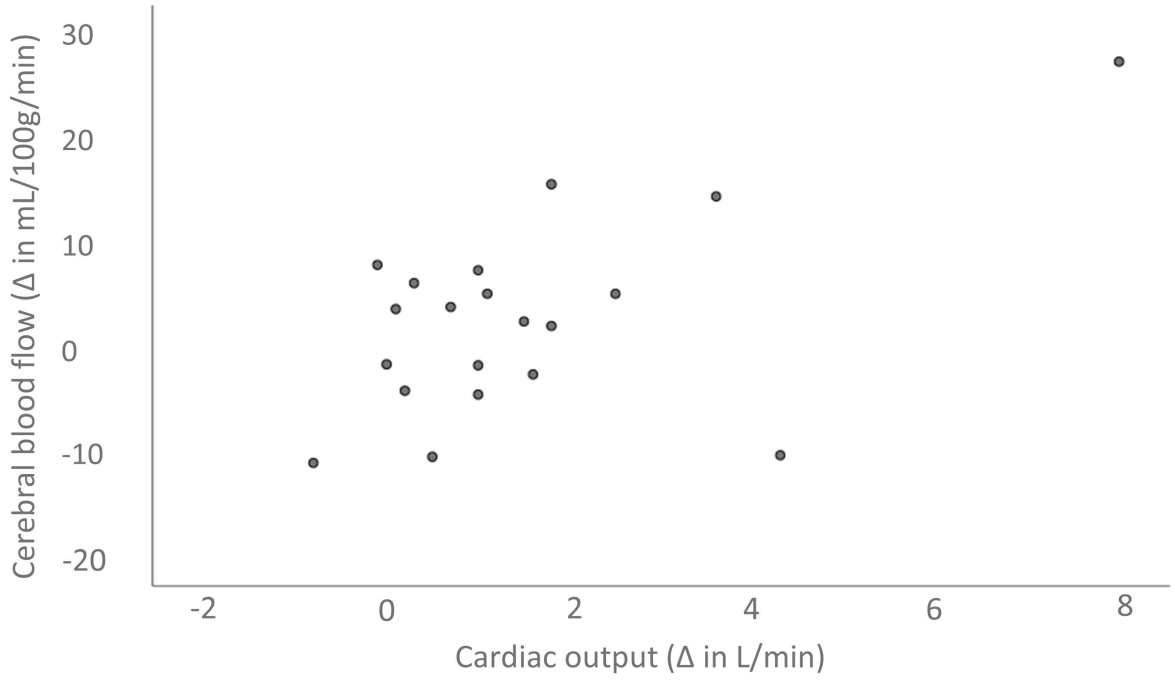
Supplementary material S2– Patient enrollment and statistical analysis

In 2018 a total 132 consecutive patients with severe aortic valve stenosis eligible to undergo TAVI were screened and approached for inclusion in the trial. A total of 37 patients met one of the exclusion criteria (n=21 had a pacemaker / ICD, n=14 had a history of structural brain disease, n=2 had a substantial language barrier). Of the remaining 95 patients, 51 refused trial participation with the majority of patients providing the explanation that the TAVI procedure itself was already stressful with extra study procedures being an additional stressor. Consequently a total of 44 patients underwent assessment of baseline cerebral blood flow using ASL. In 13 patients ASL at follow-up was not obtained due to post-TAVI pacemaker implantation (n=6), refusal of MRI follow-up (n=5) or ASL recording of insufficient quality (n=2). Accordingly, the final study population included 31 TAVI patients with complete ASL follow-up.

Categorical variables are presented as frequencies and percentages, differences between groups were tested with chi-square. Patient characteristics, and continuous values of cardiac output and cerebral blood flow were tested for normal distribution and reported as mean ± SD or median with 25th-75th percentile (Q_1-Q_3) where appropriate. Accordingly, depending on the distribution of the data, either the two-sample t-test or Mann-Whitney U test was used to determine statistically significant differences between groups. Paired sample t-tests were performed to compare differences in global and regional cerebral blood flow prior to TAVI and following TAVI. The change in cardiac output was assessed as a predictor of the increase in cerebral blood flow (Δ%) using linear regression. All statistical tests were two-tailed, and a value of $p<0.05$ was considered to indicate a statistically significant difference. Calculations were performed using SPSS software (version 25.0 for Windows, SPSS, Inc., Chicago, Illinois).

Supplementary figure 1. Scatterplot of Δ cardiac output and cerebral blood flow



Supplementary table 1. Multiple regression analysis of the increase in cardiac output

	Univariate B (SE)	P-Value	Multiple B (SE)	P-Value
Demographics				
Age (per year increase)	0.0 (0.1)	0.97	-	-
Female gender	-0.5 (0.9)	0.61	-	-
Body mass index (per kg/m^2 increase)	0.0 (0.1)	0.53	-	-
Medical history				
Previous myocardial infarction	1.6 (0.9)	0.08	0.1 (0.9)	0.93
Previous PCI	0.4 (0.5)	0.41	-	-
Previous CABG	0.6 (1.5)	0.72	-	-
Diabetes mellitus	-1.1 (0.9)	0.23	-	-
Hypertension	1.4 (0.8)	0.13	1.5 (0.6)	0.02
Dyslipidemia	0.5 (1.0)	0.64	-	-
History of coronary artery disease	0.4 (0.9)	0.64	-	-
Atrial fibrillation	1.0 (0.9)	0.28	-	-
Creatinine (per 10 µmol/L increase)	-0.4 (0.2)	0.10	-0.8 (0.2)	0.004
Baseline NYHA class (per class increase)	1.0 (1.0)	0.31	-	-
Risk scores				
EuroSCORE II (per % increase)	0.1 (0.3)	0.79	-	-
STS-PROM mortality (per % increase)	-0.3 (0.3)	0.30	-	-
Echocardiographic characteristics pre-TAVI				
Aortic max gradient (per 10 mmHg increase)	0.4 (0.3)	0.15	0.2 (0.2)	0.39
Aortic valve area (per 0.1 cm^2 increase)	2.0 (3.0)	0.52	-	-
Tricuspid regurgitation (per grade increase)[¥]	-1.0 (0.8)	0.22	-	-
Mitral regurgitation (per grade increase)[¥]	-0.3 (0.6)	0.63	-	-
Aortic regurgitation (per grade increase)[¥]	0.0 (0.5)	0.95	-	-
Procedural characteristics				
Valve size (per mm increase)	0.3 (0.2)	0.19	0.7 (0.2)	0.003

Each potential predictor, dichotomous or continuous, was tested in a univariate model and those with p<0.05 were combined in a multivariate model. B = the increase of cardiac output (in L/min), with standard error (SE). ¥graded as none/trace, mild, moderate or severe. PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, NYHA= New York Heart Association, EuroSCORE = European System for Cardiac Operative Risk Evaluation, STS-PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality

Supplementary table 2. Cerebral blood flow

	Pre-TAVI (mL/100g/min)	Post-TAVI (mL/100g/min)	Increase (%)	p Value
Overall				
Entire brain	42.5 ± 10.2	43.8 ± 9.3	6.5 ± 24.5	0.41
Left hemisphere	42.2 ± 10.3	43.3 ± 9.2	6.2 ± 24.6	0.49
Right hemisphere	42.7 ± 10.2	44.3 ± 9.8	6.8 ± 24.9	0.35
Lobes				
Left frontal	44.8 ± 11.2	45.8 ± 9.9	6.3 ± 26.7	0.59
Right frontal	45.3 ± 10.9	46.7 ± 10.4	6.2 ± 25.3	0.46
Left parietal	41.2 ± 10.0	42.8 ± 10.0	6.3 ± 23.3	0.33
Right parietal	41.7 ± 10.5	43.9 ± 10.7	8.6 ± 26.8	0.22
Left occipital	35.3 ± 11.9	36.5 ± 12.4	6.6 ± 26.6	0.41
Right occipital	35.2 ± 11.2	36.0 ± 10.6	5.5 ± 23.8	0.58
Left central	38.1 ± 9.1	38.8 ± 7.5	5.0 ± 22.2	0.67
Right central	38.3 ± 8.6	39.8 ± 8.4	6.9 ± 24.0	0.31