Supplementary material

Assessment of quantitative maps for artifacts

Four patients out of twenty-one were excluded from further analysis because the quality of the quantitative T2, T2* and consequently the resulting T2' maps was compromised by artifacts. The T2' maps of these four patients that showed a high artifact load on visual inspection are given in the Supplemental figure II. Two different methods were used to systematically analyze the presence of misleading artifacts in these patients.

1) The T2* maps were assessed for motion artifacts by calculating for each subject the empirical correlation coefficient between the data values in the respective T2* map and the T2-weighted anatomical reference (which was derived from the data acquired for T2 mapping). The rationale is that there should be a positive correlation between these data sets since contrasts are basically similar: fluid compartments yield increased T2* values and high intensities in T2-weighted anatomies, whereas iron-rich (deoxygenated hemoglobin) compartments yield local hypointensity in both data sets. In contrast, motion artifacts rather manifest themselves as spurious hyper- and hypointense structures in the T2* map which do not have a counterpart in the anatomical data, thus reducing correlations. The correlation coefficient (corr) was derived for each subject and the median value (median) and standard deviation (SD) across all values of corr was calculated. Subsequently, subjects were excluded from the analysis if corr was below a threshold which was chosen as median-SD. Data for both groups are given in the Supplemental table I.

2) In order to analyze the dispersion of the quantitative T2, T2* and T2' values as an indicator of major artifacts leading to erroneous quantitative values, we defined for each patient a region-of-interest (ROI) in the paraventricular white matter of the unaffected hemisphere which was part of the target region for analysis in all patients. As measures of skewed distribution, we extracted the SD and the coefficient of variation (CoV, SD/mean) of T2, T2* and T2' from these ROIs (Supplemental figure III) as we expected SD and CoV to be substantially higher if the data is affected by artefacts. Subjects were excluded from the analysis if SD or CoV exceeded a threshold value of median + 2 SD of the subjects without major artifacts on visual inspection.

Evaluation of PWI raw data quality and sufficiency of bolus arrival

On the whole, six patients were excluded from final anaylsis due to insufficient quality of the PWI data (two patients with poor quality data after initial evaluation and a further four patients with intermediate quality data in a second step, also see flow diagram Figure 3 in the main text).

1) After initial evaluation of the PWI timeseries, insufficient bolus arrival leading to failure of the postprocessing algorithms was suspected in two patients (sequential numbers 003 and 011). For a detailed analysis of the signal-time curve characteristics, voxels were selected from the proximal middle cerebral artery of the unaffected side to determine the shape of a potential arterial input function (AIF). Signal-time curves in these patients showed a high amount of noise in the baseline signal (Supplemental figure IV). While a slight signal decrease could be seen after arrival of the contrast agent bolus, no distinct peak was present in the timeseries (Supplemental figure IV). In order to objectify these properties, we calculated the standard deviation (SD) of the baseline signal, the signal-to-noise ratio (SNR), the amplitude of the contrast bolus-induced signal decrease and the ratio of the signal decrease divided by the SD of the baseline signal. The SNR was calculated according to a standard method given in the literature[1]. The supplemental figure V shows these characteristics for the two patients in comparison to the eleven patients that were included in the final analysis and the four patients with intermediate quality PWI data that were excluded in a second step after a more detailed evaluation. Subjects were excluded from further analysis if one of these parameters was beyond a threshold of mean ± 2 SD from the final analysis group and the intermediate quality group.

2) Since the determination of relative cerebral blood flow (rCBF) with dynamic susceptibility contrast (DSC) PWI is technically critical, we aimed to select only good quality AIFs conforming to the visual criteria specified in the Methods section of the main text. An example of an AIF complying with these criteria can be found in the Supplemental figure I. According to these criteria, a further four patients (sequential numbers 001, 015, 019 and 020) were excluded from the final analysis (flow diagram Figure 3 in the main text). Representative rCBF maps and AIFs for these patients can be found in the Supplemental figure VI. Apart from the subjective criteria, we used objective measures such as the bolus arrival time (Td), time to peak (TTP) and peak height (Pmax) to assess the AIF quality. These criteria proposed in the literature[2, 3] were complemented with additional conditions: the time of signal decrease (calculated as the time from the beginning to the maximum of the peak) and the time of signal re-increase (time from the peak maximum to re-arrival of the signal at baseline/at a stable level) as measures of steepness of the peak on both sides. Furthermore, we calculated peak width, the ratio peak height/width as a measure of peak 'sharpness' and the percentage of signal return to baseline (calculated as signal intensity post peak/signal intensity pre peak x 100 %). The eleven patients included in the final analysis (good quality AIF) had significantly shorter Td ($p<0.05$) and TTP ($p=0.001$) as well as shorter time of signal decrease ($p<0.01$), time of signal re-increase ($p<0.05$) and a smaller peak width ($p<0.05$). In addition, these patients showed a higher percentage of signal return to baseline ($p=0.006$) and a greater peak 'sharpness' ($p=0.003$) compared to the four patients that were excluded on the basis of these criteria (Supplemental table II). Pmax was larger in the final analysis group with a strong trend to significance ($p=0.078$, Supplemental figure V, C). Subjects were excluded from further analysis if one of these parameters was beyond a threshold of mean ± 2SD. Each of the four excluded patients showed mean values outside of the range mean ± 2 SD of the good quality group for at least five of these parameters. Finally, also SNR in the final analysis group was significantly higher ($p<0.05$) than in the four patients with intermediate quality AIF (Supplemental figure V, B).

Supplemental table I. Correlation coefficients of T2* maps with the anatomical reference (T2) for seventeen patients with uncompromised quantitative maps (A) and the four patients that were excluded because the T2* maps were strongly affected by artifacts (B).

A)

Sequential subject No.	Corr
001	0.322381
002	0.301653
003	0.209359
004	0.252941
005	0.172140
007	0.157517
008	0.229931
009	0.214240
010	0.271880
011	0.276973
012	0.293664
013	0.168414
014	0.233809
015	0.254706
016	0.271124
019	0.300202
020	0.240268
Median	0.233809
SD	0.085325
Lower limit (Median-SD)	0.148484

B)

Sequential subject No.	Corr
006	0.029159
017	0.012328
018	0.112011
021	0.142847

The sequential number is given for each patient. Note that correlation coefficients for each of the excluded patients in table B) are below the lower limit of median-SD of the data in table A). Corr differs significantly between the two groups (p=0.0001). Statistical significance for group differences was evaluated by using the Mann-Whitney U test for independent samples.

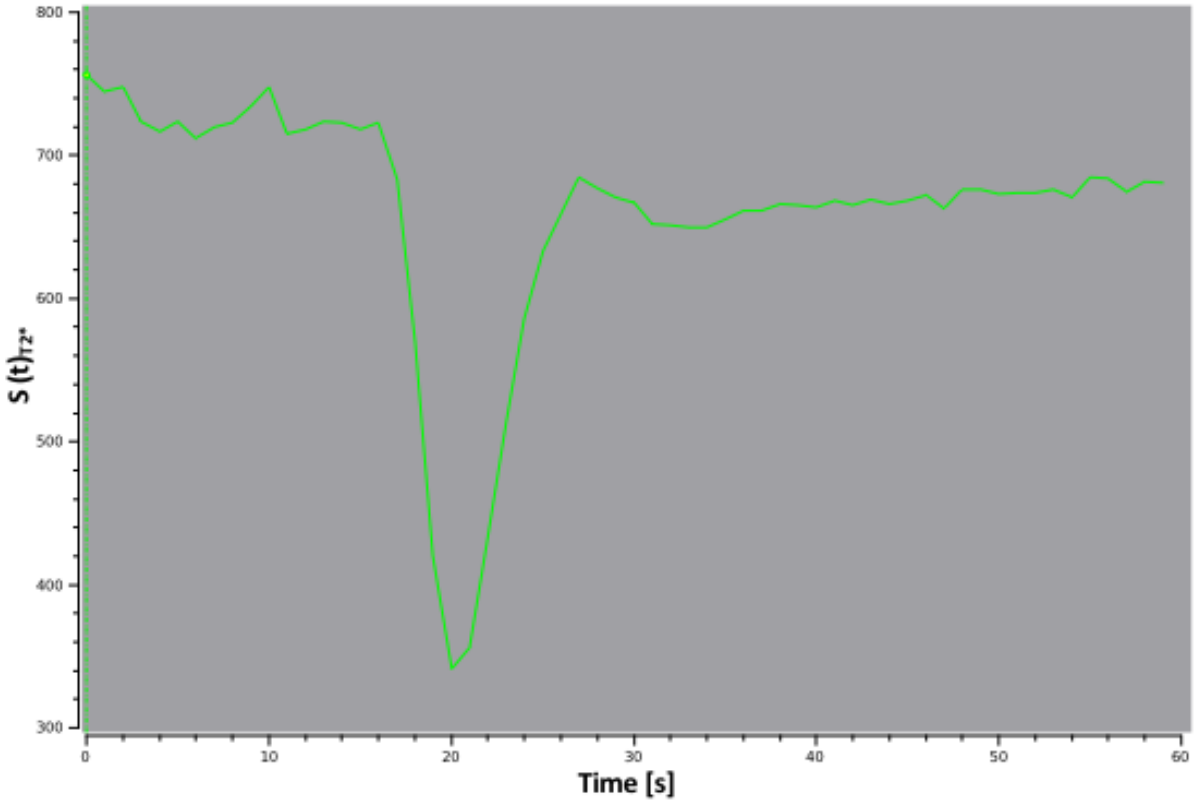
Supplemental table II. Mean values ± SD of AIF selection criteria for the final analysis group and the four patients excluded because of intermediate AIF quality.

Selection criterion	**Bolus arrival time (Td) [s]**		**Time of signal decrease [s]**		**Time of signal re-increase [s]**		**Peak width [s]**	
Patient group	Good quality (n=11)	Intermediate quality (n=4)	Good quality (n=11)	Intermediate quality (n=4)	Good quality (n=11)	Intermediate quality (n=4)	Good quality (n=11)	Intermediate quality (n=4)
Mean ±SD	20.7 ± 2.63	26.25 ± 6.08	5.46 ± 2.02	13 ± 2.83	10.09 ± 3.72	17 ± 3.61	15.64 ± 4.78	25.75 ± 8.06
p-value	0.036		0.003		0.022		0.040	

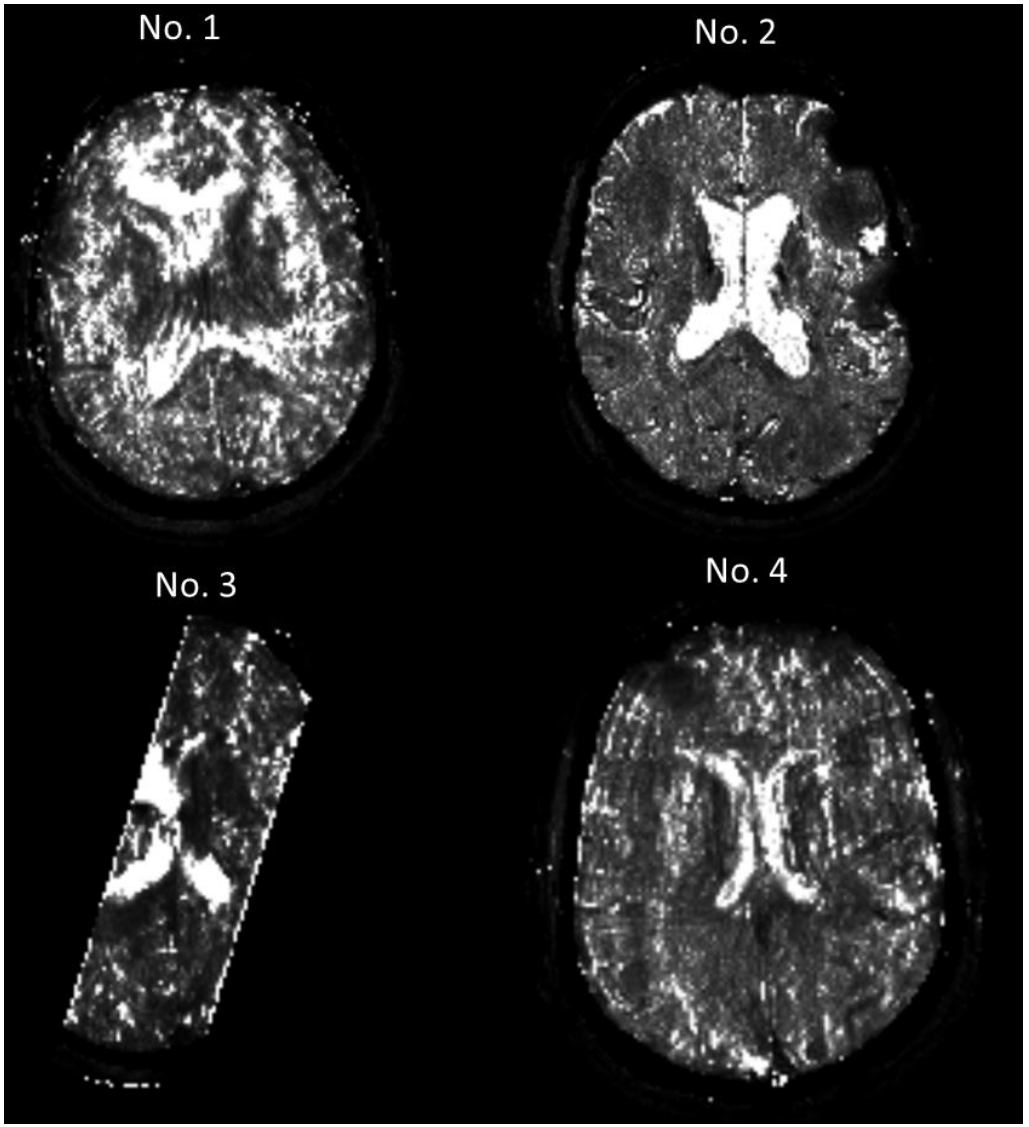
Selection criterion	**Time to peak (TTP) [s]**		**Peak 'sharpness' (height/width) [s^{-1}]**		**Signal return to baseline [%]**	
Patient group	Good quality (n=11)	Intermediate quality (n=4)	Good quality (n=11)	Intermediate quality (n=4)	Good quality (n=11)	Intermediate quality (n=4)
Mean ± SD	24.27 ± 7.91	39.25 ± 7.27	21.66 ± 8.86	8.11 ± 2.02	93.17 ± 4.29	80.05 ± 7.58
p-value	0.001		0.003		0.006	

s: seconds. Statistical significance for group differences was evaluated by using the Mann-Whitney U test for independent samples.

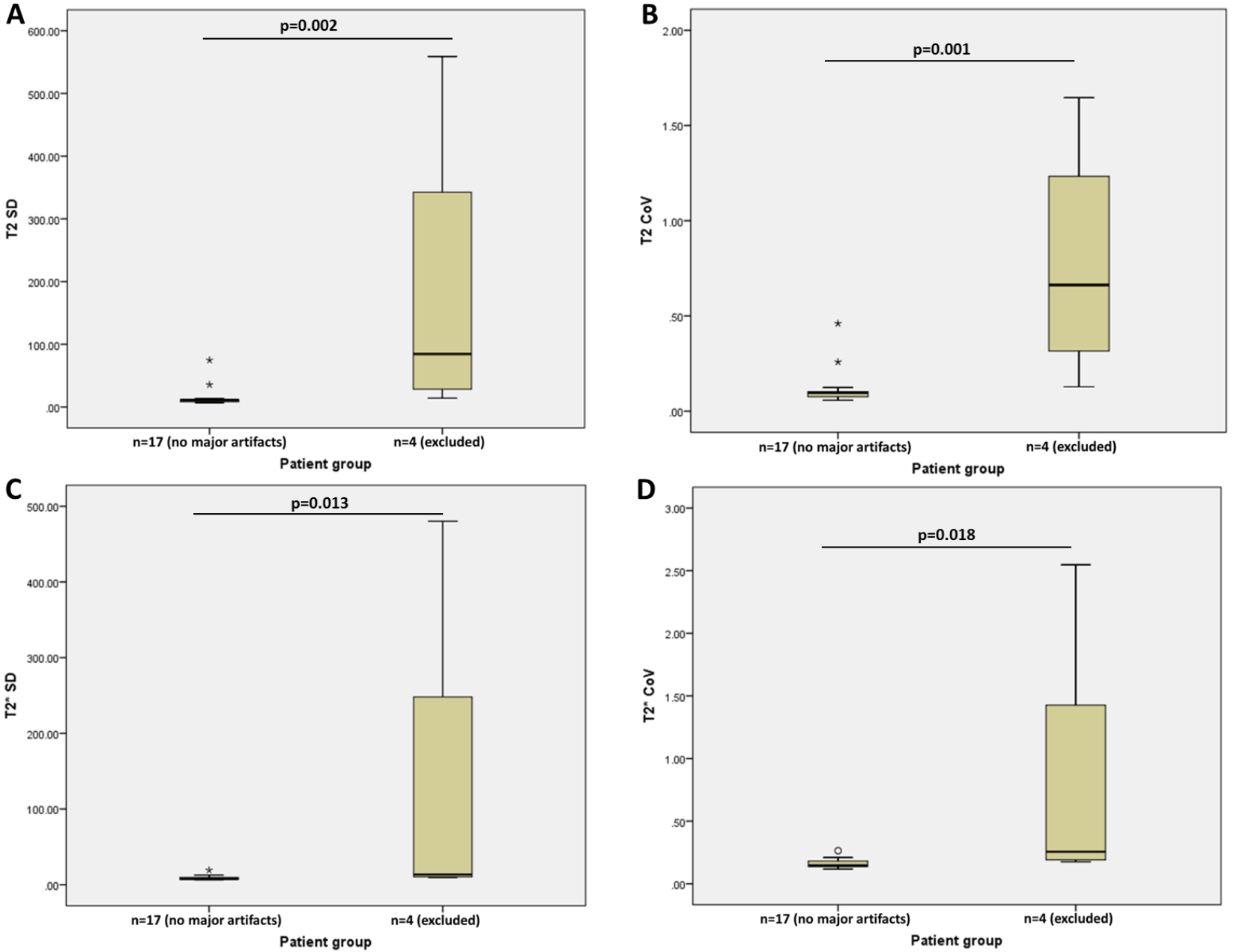
Supplemental figures

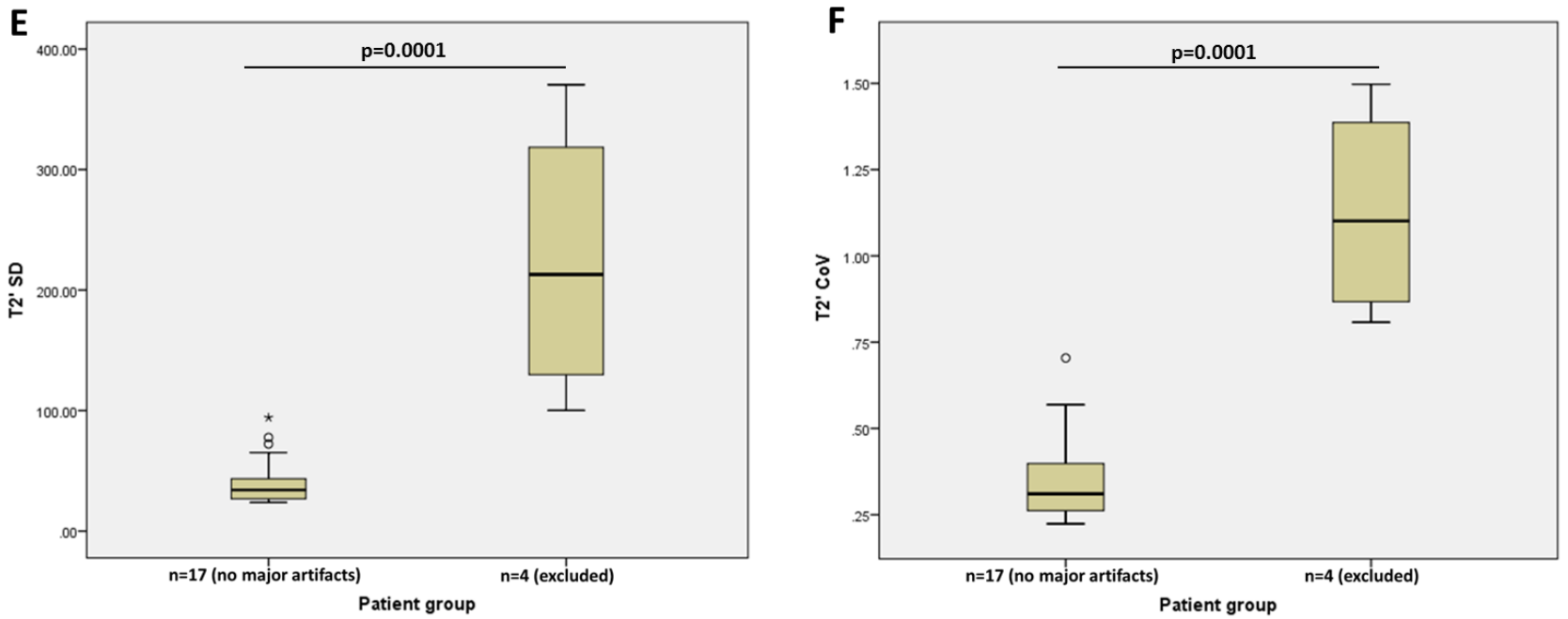


Supplemental figure I. Example of a signal-time curve (arbitrary units) used as an AIF for a representative patient. Note the sharp and distinct peak and the relatively low baseline noise level. t: time; s: seconds.

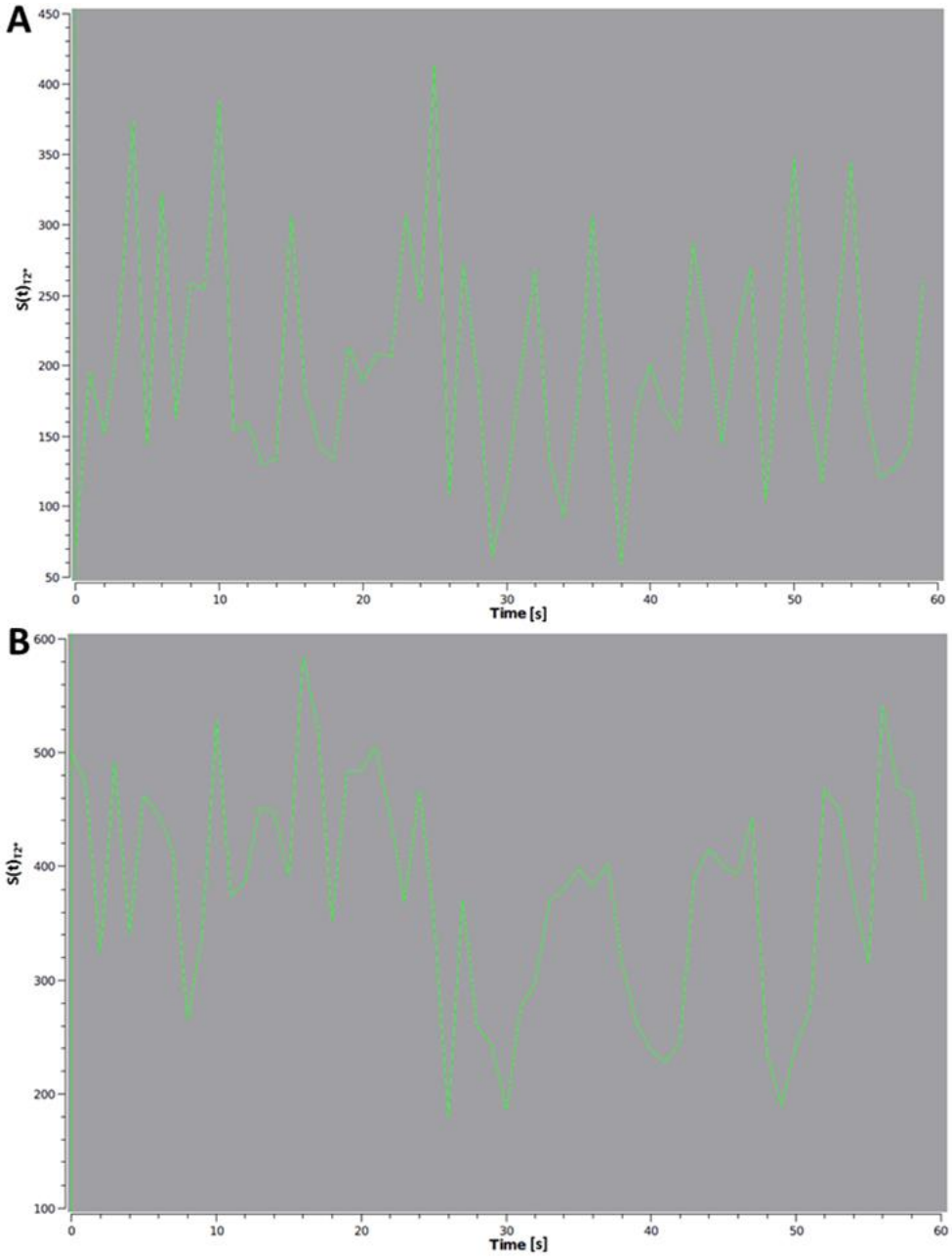

No. 1
No. 2
No. 3
No. 4

Supplemental figure II. T2' maps of the four patients (sequential numbers given in the Supplemental table B) that were excluded due to major artifacts. Note the pronounced blurring of anatomical structures and the presence of variantly occurring hypo- and hyperintensities. In No.3, the impact of motion-related artifacts on the quantitative T2 and T2* data was very pronounced and resulted in a failure of the coregistration of T2 to T2*, leading to an incomplete representation of brain structures on the T2' map.

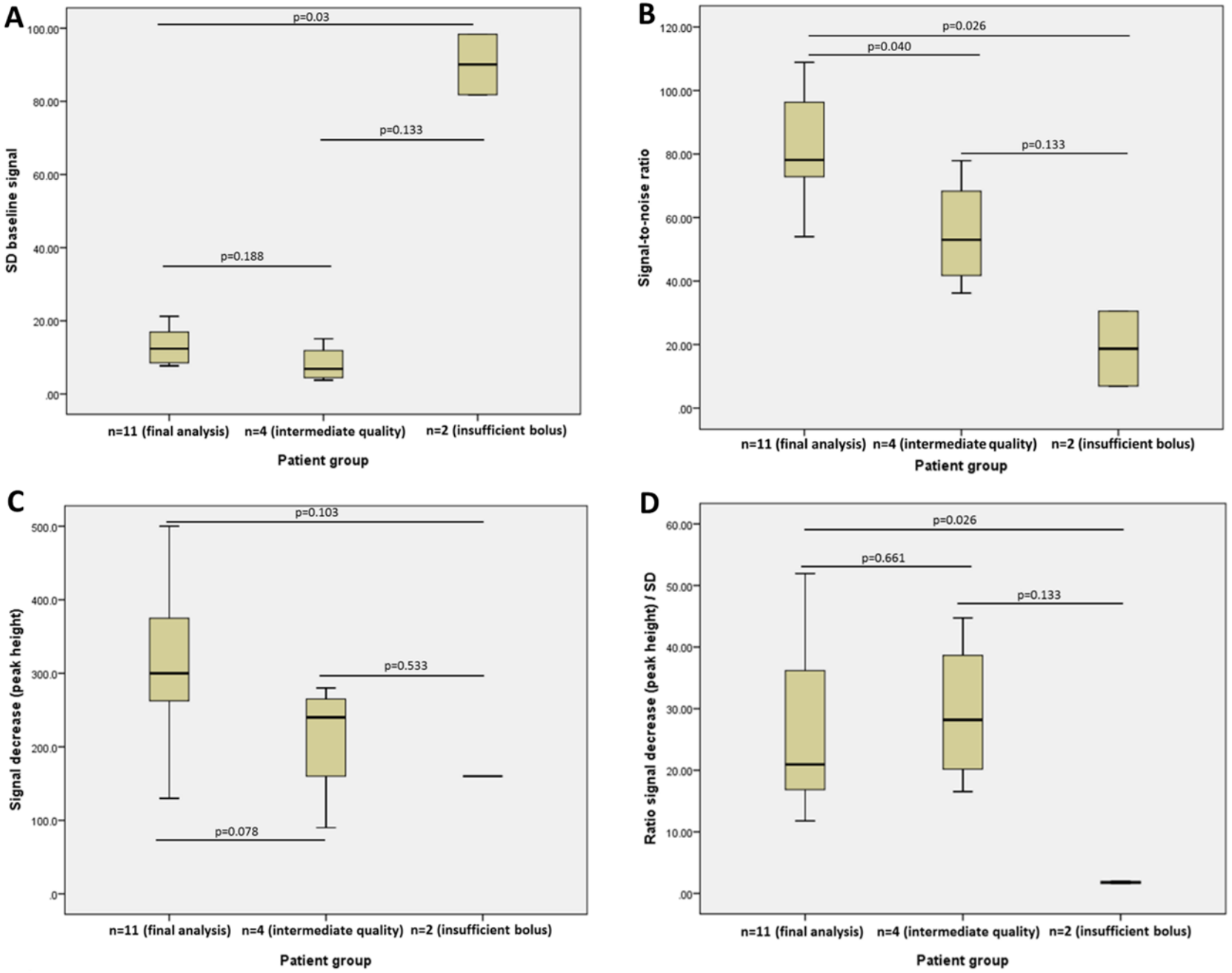

A
p=0.002
T2 SD
600.00
500.00
400.00
300.00
200.00
100.00
.00
n=17 (no major artifacts)
n=4 (excluded)
Patient group
B
p=0.001
T2 CoV
2.00
1.50
1.00
.50
.00
n=17 (no major artifacts)
n=4 (excluded)
Patient group
C
p=0.013
T2* SD
500.00
400.00
300.00
200.00
100.00
.00
n=17 (no major artifacts)
n=4 (excluded)
Patient group
D
p=0.018
T2* CoV
3.00
2.50
2.00
1.50
1.00
.50
.00
n=17 (no major artifacts)
n=4 (excluded)
Patient group



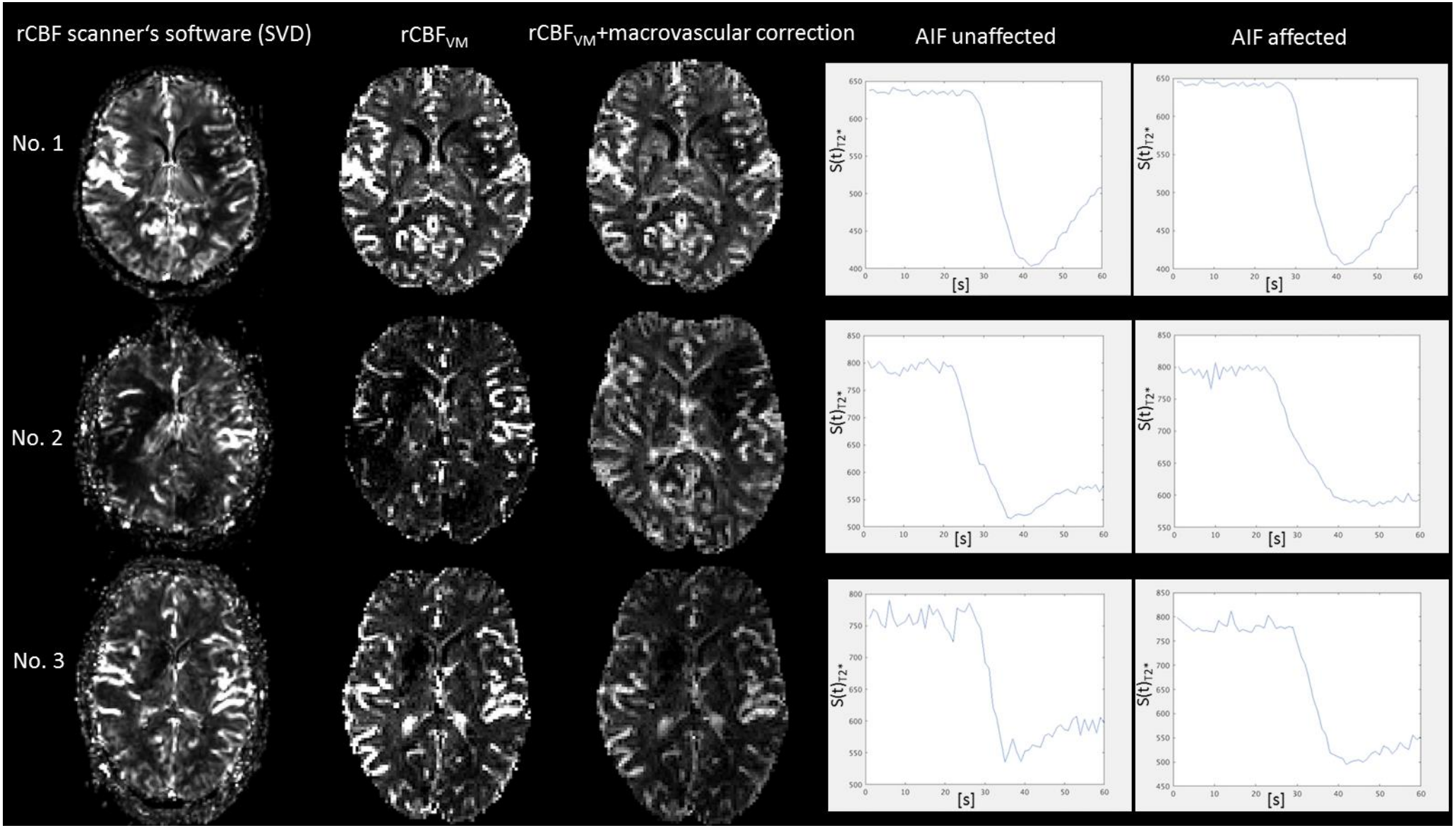
Supplemental figure III. Boxplots displaying standard deviations (SD, given in milliseconds) and coefficients of variation of T2, T2* and T2' for the four patients with strongly motion-affected quantitative imaging data and the patients without major artifacts on visual inspection. For these measurements, quantitative maps were used without any threshold. SD and CoV of each parameter were significantly higher for the excluded patients indicating a more skewed distribution of values due to a strong influence of artifacts leading to erroneous values. Statistical significance for group differences was evaluated by using the Mann-Whitney U test for independent samples.

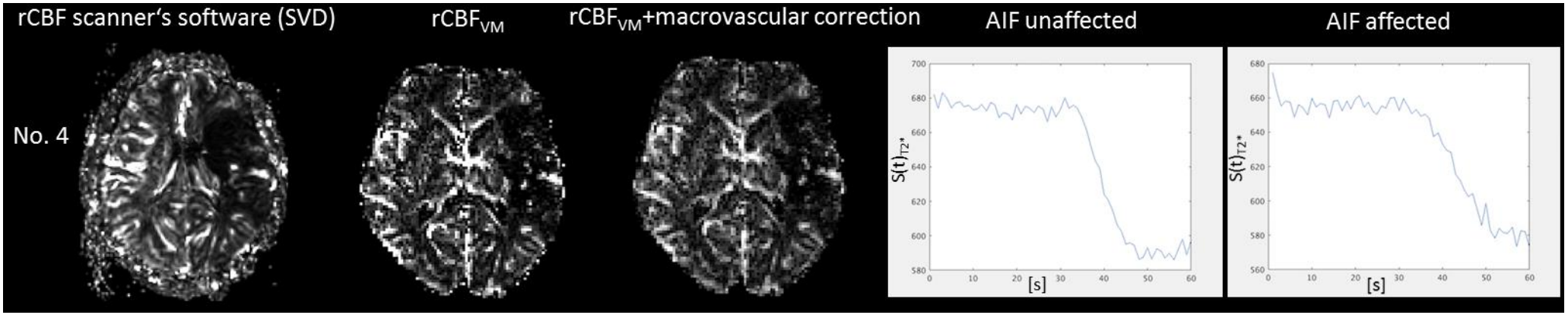

A
450
400
350
300
250
200
150
100
50
S(t)I2*
0
10
20
30
40
50
60
Time [s]
B
600
500
400
300
200
100
S(t)I2*
0
10
20
30
40
50
60
Time [s]

Supplemental figure IV. Signal-time curves for the initially excluded two patients with insufficient bolus arrival. A high level of noise is evident and while a small Gadolinium-induced signal decrease is visible, no distinct peak is present. Signal intensities are given in arbitrary units. s: seconds.

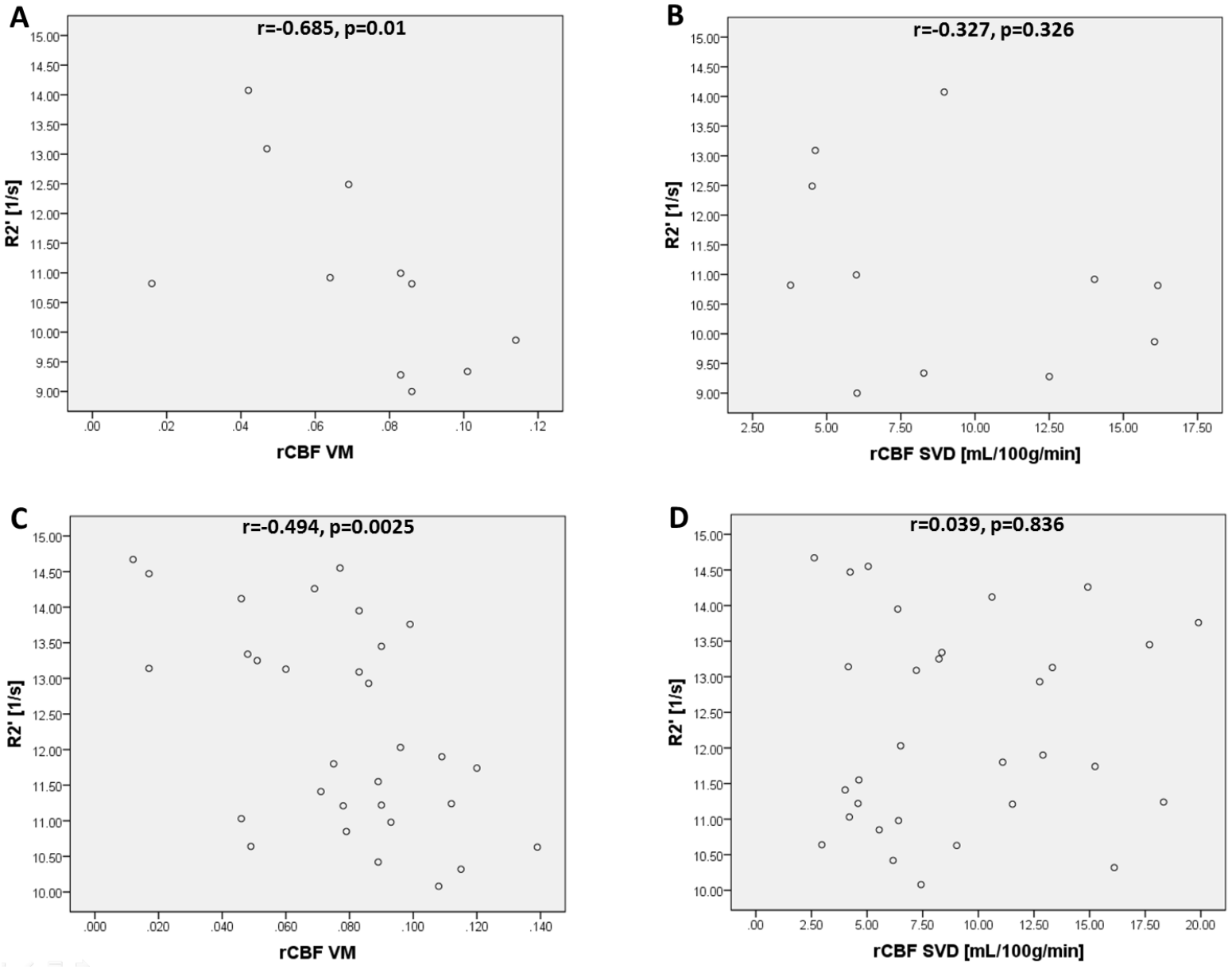

A
SD baseline signal
100.00
80.00
60.00
40.00
20.00
.00
p=0.03
p=0.133
p=0.188
n=11 (final analysis)
n=4 (intermediate quality)
n=2 (insufficient bolus)
Patient group
B
Signal-to-noise ratio
120.00
100.00
80.00
60.00
40.00
20.00
.00
p=0.026
p=0.040
p=0.133
n=11 (final analysis)
n=4 (intermediate quality)
n=2 (insufficient bolus)
Patient group
C
Signal decrease (peak height)
500.0
400.0
300.0
200.0
100.0
.0
p=0.103
p=0.533
p=0.078
n=11 (final analysis)
n=4 (intermediate quality)
n=2 (insufficient bolus)
Patient group
D
Ratio signal decrease (peak height) / SD
60.00
50.00
40.00
30.00
20.00
10.00
.00
p=0.026
p=0.661
p=0.133
n=11 (final analysis)
n=4 (intermediate quality)
n=2 (insufficient bolus)
Patient group

Supplemental figure V. Boxplots for different characteristics of the PWI signal-time curves stratified according to the different patient groups (patients excluded initially (n=2), excluded after detailed AIF evaluation (n=4) and patients included in the final analysis (n=11)). The mean values for the SD of the baseline signal and the ratio signal decrease / SD of the baseline signal from the initially excluded two patients was beyond the range mean ± 2 SD of the final analysis and the intermediate quality group (panels A and D), indicating a high level of baseline noise and that the amplitude of the contrast bolus-induced signal decay in these patients was not appreciably larger than the amplitude of the baseline noise. Parameters differed significantly between the two patients with insufficient bolus and the final analysis group, except for the amplitude of the signal decrease (peak height for the final analysis and the intermediate quality group, panel D). Values (calculated from signal intensities) in panels A, C and D are given in arbitrary units. Statistical significance for group differences was evaluated by using the Mann-Whitney U test for independent samples. SD: standard deviation.

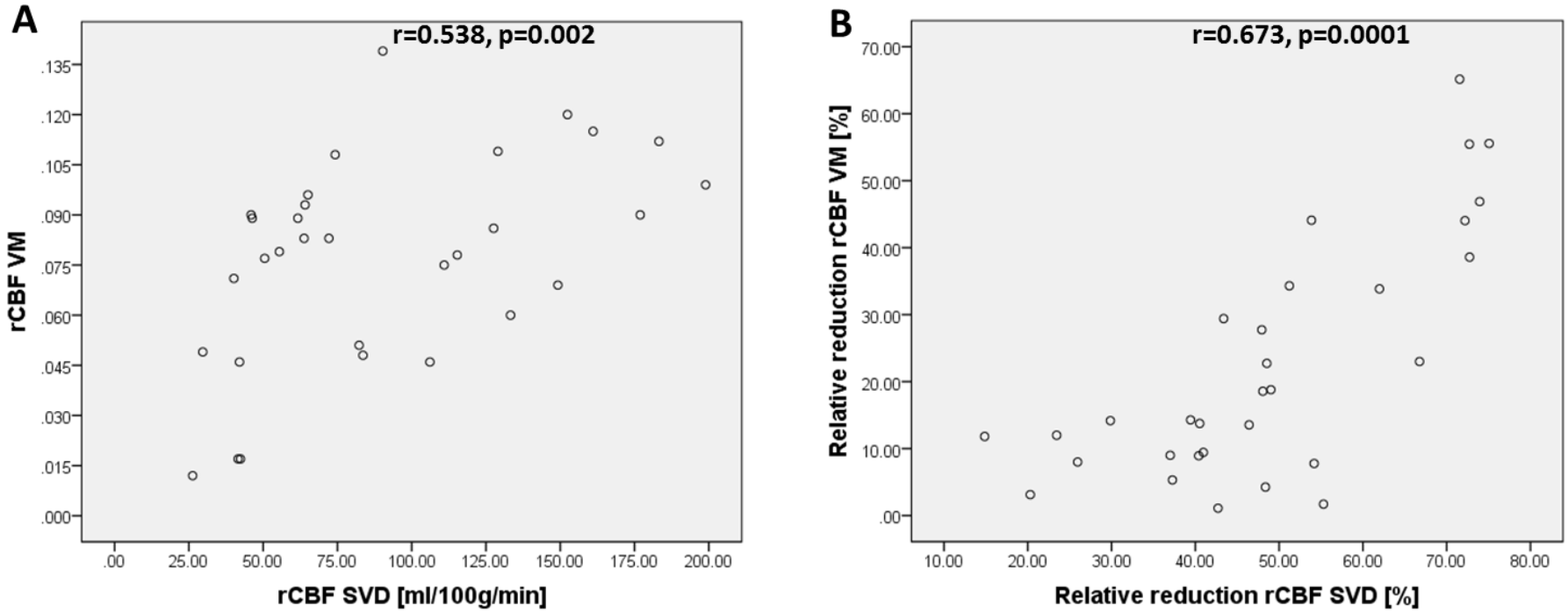

rCBF scanner‘s software (SVD)
rCBF$_{VM}$
rCBF$_{VM}$+macrovascular correction
AIF unaffected
AIF affected
No. 1
No. 2
No. 3
S(t)$_{T2*}$
[s]



Supplemental figure VI. Maps of deconvolved rCBF and rCBF calculated using the vascular model (with and without correction for macrovascular components) as well as arterial input functions for the affected and unaffected side for the 4 patients that were excluded from final analysis based on a detailed quantitative analysis of signal-time curve characteristics. Signal intensity is given in arbitrary units. rCBF: relative cerebral blood flow; VM: vascular model; SVD: singular value deconvolution; AIF: arterial input function; s: seconds.


A
r=-0.685, p=0.01
R2' [1/s]
rCBF VM
B
r=-0.327, p=0.326
R2' [1/s]
rCBF SVD [mL/100g/min]
C
r=-0.494, p=0.0025
R2' [1/s]
rCBF VM
D
r=0.039, p=0.836
R2' [1/s]
rCBF SVD [mL/100g/min]

Supplemental figure VII. R2' values from ROIs of the entire (A, B) and the subdivided (C, D) mismatch area plotted against $rCBF_{VM}$ and $rCBF_{SVD}$ values. Significant correlations were found between R2' and $rCBF_{VM}$. rCBF: relative cerebral blood flow; VM: vascular model; SVD: singular value deconvolution; ms: milliseconds; s: seconds; mL: milliliters; g: grams; min: minute.



Supplemental figure VIII. Relationship between conventional $rCBF_{SVD}$ and $rCBF_{VM}$ based on the vascular model within the ROIs defined by subdivision of the mismatch area. A: $rCBF_{VM}$ values plotted against $rCBF_{SVD}$ values. B: scatterplot of the relative rCBF reduction within hypoperfused tissue, given in %reduction in relation to the respective corresponding contralateral area in the unaffected hemisphere. rCBF: relative cerebral blood flow; VM: vascular model; SVD: singular value deconvolution; mL: milliliters; g: grams; min: minute.

Supplemental references

1. Firbank MJ, Harrison RM, Williams ED and Coulthard A. Quality assurance for MRI: practical experience. *Br J Radiol*. 2000; 73: 376-83.
2. Bjornerud A and Emblem KE. A fully automated method for quantitative cerebral hemodynamic analysis using DSC-MRI. *J Cereb Blood Flow Metab*. 2010; 30: 1066-78.
3. Crane DE, Donahue MJ, Chappell MA, et al. Evaluating quantitative approaches to dynamic susceptibility contrast MRI among carotid endarterectomy patients. *J Magn Reson Imaging*. 2013; 37: 936-43.