SUPPLEMENTAL ONLINE DATA

Value of Immediate Flat-Panel Perfusion Imaging After Endovascular Therapy (AFTERMATH): A proof of concept study

Table of Contents

Method S1 Image Acquisition and Perfusion Post-Processing

Image Acquisition

Out of the ten sweeps, the first two rotations served as a mask run with the following eight being used to record inflow and outflow of contrast agent (60 ml Iopamiro 400 or 300), creating time–density curves with eight time points. Contrast agent injection via an 18 G cubital venous line was started simultaneously with the first mask run. All contrast agents were flushed with saline (40 – 60 ml) with an injection rate of 5 ml/s via a dual-head power injector. Each acquired rotation was reconstructed individually using the filtered back projection algorithm available on the clinical system (ARTIS icono VE20, Siemens Healthineers, Forchheim, Germany). The reconstruction algorithm includes system-specific steps to correct for scatter radiation, beam hardening, projection image truncation and ring artifacts.[1] The reconstruction parameters were 0.48mm voxel size, 512x512 matrix, 378 slices, 0.48mm slice thickness and reconstruction kernel "HU Normal".

Perfusion post-processing

First, 3D-3D registration was performed between the first acquired volume and all remaining volumes to compensate for potential head motion during the acquisition. Accordingly, all volumes were automatically aligned to orbitomeatal line and spatially resampled to 0.96mm voxel size. The two mask volumes were used to subtract the anatomical background from the remaining 8 contrasted volumes. Noise reduction via non-linear filtering was performed on the contrasted subtracted volumes.[2] Time-concentration curves with a temporal sampling of 1s were extracted from the subtracted volume series by resampling via temporal spline interpolation. Afterwards, an automated detection of the arterial input function was performed and voxels containing air, bone or vascular structures were excluded by thresholding. Perfusion maps were computed using deconvolution-based perfusion analysis.[3] Finally, all computed perfusion maps were stored in a 16bit raster data format for visualization in the 3D Slicer software. Estimated duration for processing and analyzing was 90 seconds (30 seconds for reconstruction and 60 seconds for further perfusion analysis).

Table S1 Locations of the Occlusion on the DSA and FPCTP Imaging

Region	**Frontal**	**Parietal**	**Temporal**	**Occipital**
Areas	Orbitofrontal	Anterior parietal	Anterior temporal	Angular
	Prefrontal	Posterior parietal	Middle temporal	Temporo-occipital
	Precentral	Postcentral	Posterior temporal	
	Central			

DSA – digital subtraction angiography; FPCTP – flat-panel computed tomography perfusion.

Table S2 Additional Baseline and Interventional Characteristics

Variables	**N = 26[a]**
BASELINE	
Onset-To-Door (h)	3.3 (2.1, 7.9)
Occlusion sites	
ICA	1 (3.8%)
M1 – MCA	19 (73%)
M2 – MCA	6 (23%)
INTERVENTION	
Intravenous thrombolysis	7 (27%)
First-line technique	
Stent retriever	15 (57.7%)
Aspiration	1 (3.8%)
Stent retriever with aspiration	10 (38.5%)
Number of device passes	2 (1, 3)
ASITN/SIR collaterals score	
1	7 (27%)
2	6 (23%)
3	10 (38%)
4	3 (12%)
OUTCOME	
Hypoperfusion volume on FPCTP (ml)	55 (7.6 – 130.1)
Intracranial hemorrhage	0 (0%)
[a]Median (IQR); n (%)	

ICA: internal carotid artery; MCA: middle cerebral artery; ASITN/SIR: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; FPCTP: flat-panel computed tomography perfusion imaging.

Table S3 Baseline and Intervention Characteristics of Patients Without and With FPCTP During The Study Period

	Entire Cohort	Without FPCTP	With FPCTP	p
n	251	225	26	
Age (median [IQR])	74 [63, 82]	74 [63, 81]	77 [61, 83]	0.528
Sex = Male (%)	132 (52.6)	114 (50.7)	18 (69.2)	0.112
Atrial fibrillation = Yes (%)	93 (37.8)	82 (36.9)	11 (45.8)	0.527
Coronary heart disease = Yes (%)	48 (19.7)	43 (19.5)	5 (20.8)	1
Diabetes = Yes (%)	40 (16.4)	33 (15.0)	7 (29.2)	0.136
Hyperlipidemia = Yes (%)	164 (67.2)	151 (68.6)	13 (54.2)	0.228
Hypertension = Yes (%)	172 (70.5)	155 (70.5)	17 (70.8)	1
Smoking status = Yes (%)	60 (23.9)	54 (24.0)	6 (23.1)	1
NIHSS on admission (median [IQR])	12 [6, 18]	11 [5, 17]	15 [11, 20]	0.074
Onset-To-Door (h) (median [IQR])	3.3 [1.8, 7.6]	3.3 [1.8, 7.6]	3.3 [2.1, 7.9]	0.722
Occlusion sites (%)				0.056
ICA	34 (15.3)	33 (16.8)	1 (3.8)	
M1 - MCA	114 (51.4)	95 (48.5)	19 (73.1)	
M2 - MCA	74 (33.3)	68 (34.7)	6 (23.1)	
Intravenous Thrombolysis = Yes (%)	86 (34.3)	79 (35.1)	7 (26.9)	0.539
Number of device passes (median [IQR])	1 [1, 3]	1 [1, 3]	2 [1, 3]	0.099
ASITN/SIR Collaterals Score (%)				0.235
0	21 (9.9)	21 (10.5)	0 (0.0)	
1	30 (14.1)	26 (13.0)	7 (26.9)	
2	44 (20.7)	43 (21.5)	6 (23.1)	
3	96 (45.1)	89 (44.5)	10 (37.8)	
4	22 (10.3)	21 (10.5)	3 (12.2)	
TICI (%)				0.299
0	2 (0.8)	2 (0.9)	0 (0.0)	
1	1 (0.4)	1 (0.4)	0 (0.0)	
2a	9 (3.6)	8 (3.6)	1 (3.8)	
2b	74 (29.5)	65 (28.9)	9 (34.7)	
3	165 (65.7)	149 (66.2)	16 (61.5)	
Intracranial hemorrhage = Yes (%)	8 (3.3)	8 (3.6)	0 (0.0)	0.729
90-Day mRS (%)				0.173
0	60 (24.3)	58 (26.2)	2 (7.7)	
1	59 (23.9)	51 (23.1)	8 (30.8)	
2	38 (15.4)	36 (16.3)	2 (7.7)	
3	25 (10.1)	21 (9.5)	4 (15.4)	
4	16 (6.5)	13 (5.9)	3 (11.5)	
5	15 (6.1)	14 (6.3)	1 (3.8)	
6	34 (13.8)	28 (12.7)	6 (23.1)	

FPCTP – flat-panel computed tomography perfusion; NIHSS: National Institutes of Health Stroke Scale; ICA: internal carotid artery; MCA: middle cerebral artery; ASITN/SIR: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; TICI: treatment in cerebral infarction as evaluated by the operator; mRS: modified Rankin Scale.

Table S4 Core-lab Versus Operator Reperfusion Grading

Case	Operator TICI score	Core-lab eTICI score	Operator overestimation*
1	2b	2b67	
2	3	3	
3	2b	2b67	
4	2b	2b50	
5	3	2c	+
6	3	2c	+
7	3	2c	+
8	3	3	
9	2b	2b67	
10	2b	2b67	
11	3	3	
12	3	2b67	+
13	3	2b67	+
14	3	3	
15	3	3	
16	2b	2b50	
17	3	2b67	+
18	3	2c	+
19	2b	2b67	
20	3	3	
21	3	2c	+
22	3	2b67	+
23	2a	2a	
24	3	3	
25	2b	2a	+
26	2b	2b67	

*in comparison to the core-lab

TICI – Thrombolysis in Cerebral Infarction; eTICI – expanded Thrombolysis in Cerebral Infarction.

Table S5 Outcome Characteristics of the Study Population Stratified by TICI Score (Operator)

	NIHSS at 24 hours		
Variable	Unadjusted Odds Ratios	95% CI	P-Value
TICI*	0.44	0.12 – 1.39	0.17
	mRS score at 3 months		
TICI*	0.32	0.09 – 1.07	0.06
	mRS score 0-2 at 3 months		
TICI†	3.82	0.88 – 22.35	0.09

CI – confidence interval; TICI - Treatment in Cerebral Ischemia; NIHSS - National Institutes of Health Stroke Scale; mRS - Modified Rankin Scale. Unadjusted *ordinal and †logistic regressions were used to test for associations between clinical outcomes and operator-rated reperfusion grades. All point estimated suggested numerically better outcomes with better reperfusion scores, without reaching statistical significance.

Table S6 Outcome Characteristics of the Study Population Stratified by eTICI Score (Core-lab)

	NIHSS at 24 hours		
Variable	Unadjusted Odds Ratios	95% CI	P-Value
eTICI*	0.60	0.33 – 1.06	0.08
	mRS score at 3 months		
eTICI*	0.78	0.47 – 1.30	0.33
	mRS score 0-2 at 3 months		
eTICI†	1.65	1.01 – 4.25	0.04

CI – confidence interval; eTICI - expanded Treatment in Cerebral Ischemia; NIHSS - National Institutes of Health Stroke Scale; mRS - Modified Rankin Scale. Unadjusted *ordinal and †logistic regressions were used to test for associations between clinical outcomes and core-lab-rated reperfusion grades. There was a significant association between increasing reperfusion grade (core-lab) and achieving functional independence (mRS score 0-2) at 3 months after stroke.

Table S7 Outcome Characteristics of the Study Population Stratified by the Presence of Absence of a Perfusion Deficit on FPCTP

Outcome	Overall	No deficit on FPCTP	Perfusion deficit on FPCTP	p
n	26	6	20	
NIHSS at 24hours (median [IQR])	6 [2, 15]	2 [1, 5]	8 [5, 18]	0.08
mRS at 3 months (median [IQR])	3 [1, 5]	1 [0, 2]	3 [1, 5]	0.06
mRS 0-2 at 3 months (%)	13 (50.0)	5 (83.3)	8 (40.0)	0.16

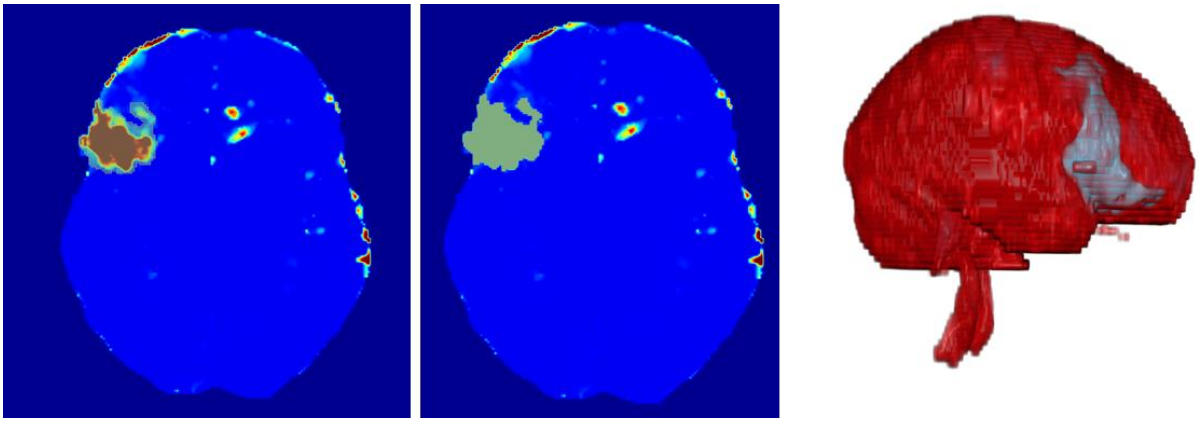
NIHSS - National Institutes of Health Stroke Scale; mRS - Modified Rankin Scale; FPCTP - flat-panel computed tomography perfusion imaging. All results suggested numerically better outcomes with no deficit on FPCTP, without reaching statistical significance.

Table S8 Ordinal Regression Analysis With Hypoperfusion Volume

	Modified Rankin Scale Score at 90-Day		
Predictors	Adjusted Odds Ratios*	95% CI	P-Value
Age	1.04	1.00 – 1.10	0.05
NIHSS at admission	1.16	1.03 – 1.32	0.02
Hypoperfusion volume (ml)	5.27	1.53 – 21.13	0.01
*>1 indicating unfavorable shift on the Modified Rankin Scale Score			

CI - confidence interval; NIHSS - National Institutes of Health Stroke Scale; FPCTP - flat-panel computed tomography perfusion imaging. Median volume of hypoperfused tissue on FPCTP was 55 ml (IQR 7.59 – 130.10 ml). Hypoperfusion volume was logarithmically transformed and odds ratios for hypoperfusion volume should be interpreted for logarithmically transformed 1ml volume increase. Patients with higher volumes of residual hypoperfusion had worse mRS scores at 90 days.

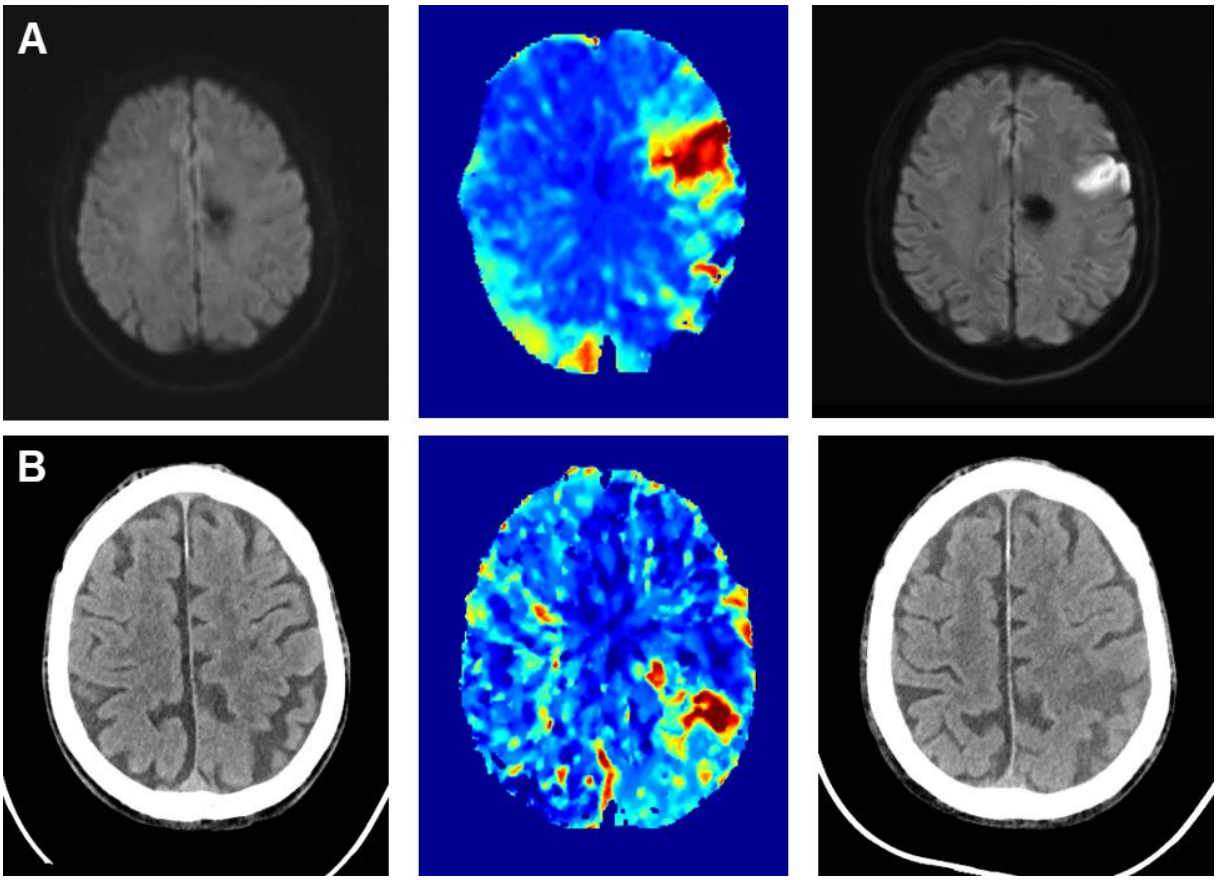
Figure S1 Segmentation of Hypoperfused Tissue



Left-Panel: All segmentations of residual hypoperfusions were performed with manual delineation of the hypoperfused brain tissue on resampled 3mm axial slices of Tmax perfusion maps. No treshholds were used for the final segmentation volume. Middle-Panel: Opaque area presents segmented residual hypoperfused tissue after the intervention. Right-Panel: 3D volume rendering of segmented residual hypoperfusion (shown in light blue).

Segmentation was performed with the same software that was used for data visualization (3D Slicer v5.2.2, Boston, Massachusetts, USA).[4] Following functions in 3D Slicer were used: Resample Scalar Volume, Colors and Segment Editor. Segmentation was performed with the "Draw" option where editable area was the volume of the entire brain. Editable intensity range was predefined to exclude background zone outside of the brain volume.

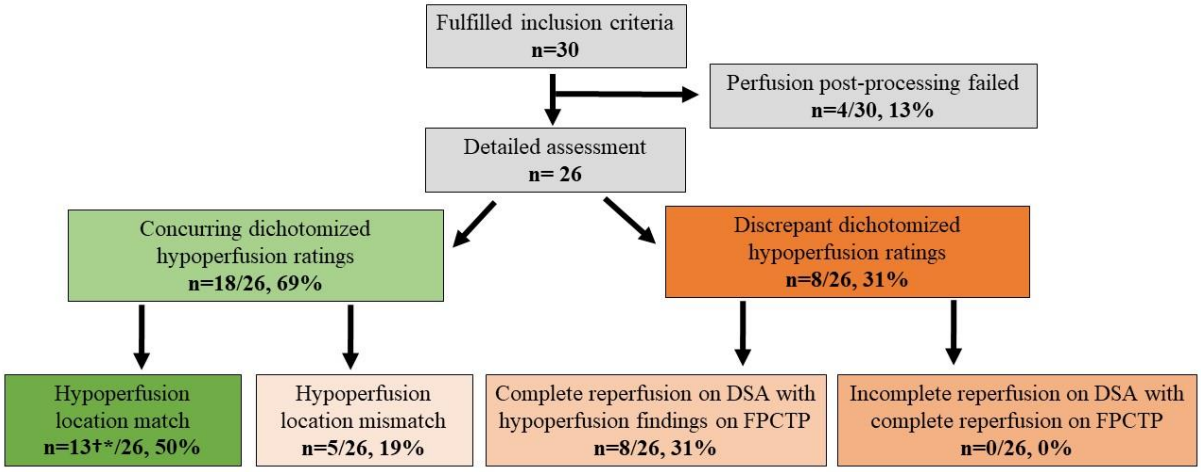
Figure S2 New Infarct on Follow-up Imaging



MRI – magnet resonance imaging; FPCTP - flat-panel computed tomography perfusion imaging; NCCT – non-contrast computed tomography (A) Admission MRI of a patient with left-side M1 occlusion without developed infarct at the time of admission imaging. Immediate post-interventional FPCTP shows residual hypoperfusion. Follow-up MRI at 24 hours shows newly infarcted tissue directly corresponding to the area of residual hypoperfusion from FPCTP which was not seen on admission imaging. (B) Admission NCCT of a patient with left-side M2 occlusion without developed infarct at the time of admission imaging. Immediate post-interventional FPCTP shows residual hypoperfusion. Follow-up NCCT at 24 hours shows newly infarcted tissue directly corresponding to the area of residual hypoperfusion from FPCTP which was not seen on admission imaging.

All patients undergo follow-up imaging 24 hours after the intervention per institution's protocols. Admission and follow-up imaging was used to qualitatively assess presence of final infarct lesion. Hypoperfusion between FPCTP and infarct on follow-up imaging was rated as concordant if the area of hypoperfusion from FPCTP directly corresponded to the area of infarct on follow-up imaging. Locations and regions from Table S1 were used to confirm concordance between hypoperfusion from FPCTP and infarcted area from follow-up imaging. Admission imaging was used to exclude areas that have undergone infarction prior to the intervention. There were no cases with large infarcts on admission in the present cohort.

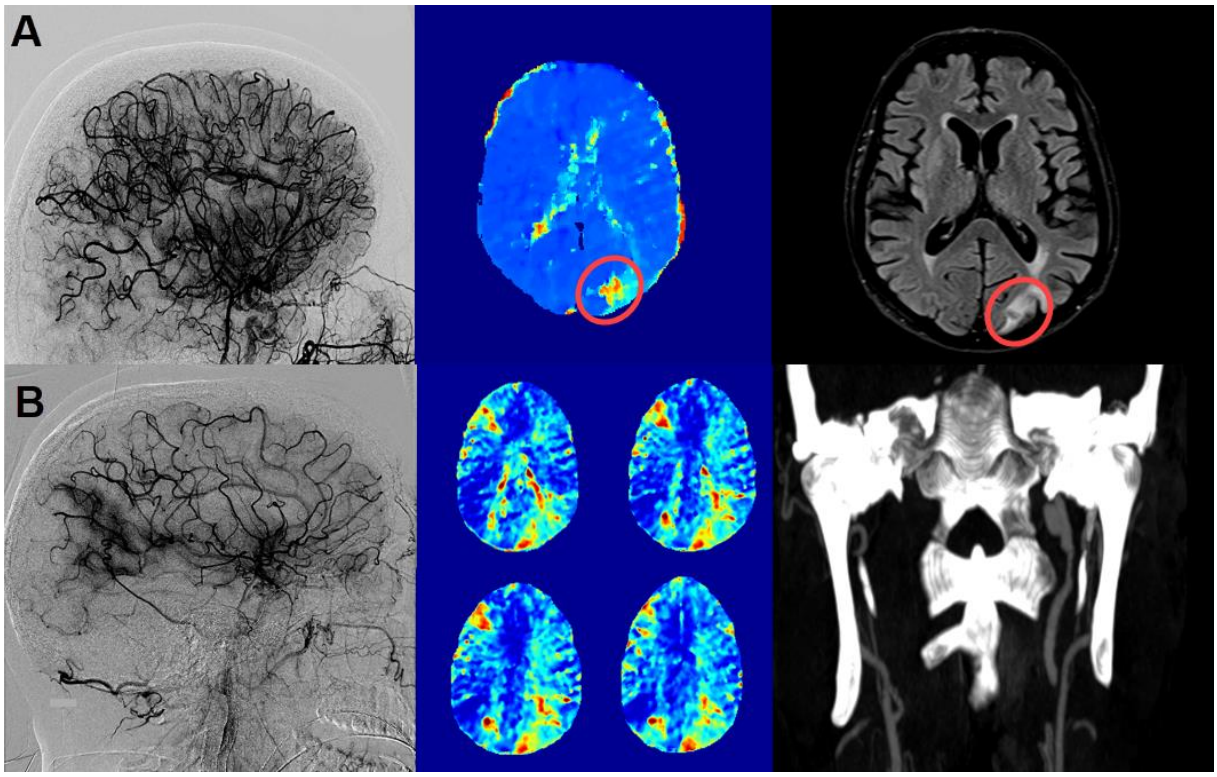
Figure S3 Group Allocation Based on Operator-Graded TICI Score



† In two cases there was hypoperfusion detected on the contralateral side of the mechanical thrombectomy target occlusion on FPCTP.
* In one case there was hypoperfusion detected on the contralateral side of the mechanical thrombectomy target occlusion on FPCTP.

DSA – digital subtraction angiography; FPCTP – flat-panel computed tomography perfusion imaging

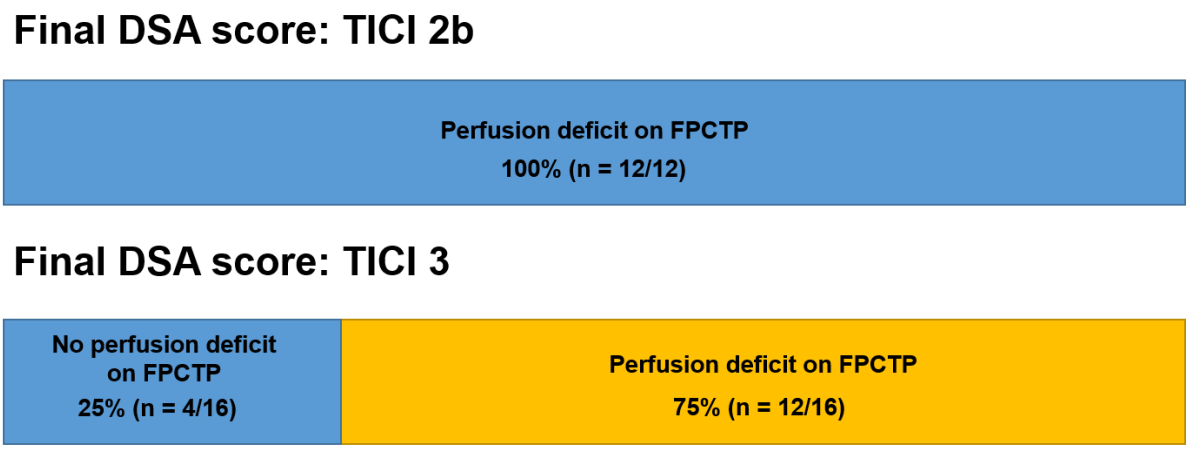
Figure S4 Contralateral Hypoperfusion



DSA - digital subtraction angiography; FPCTP - flat-panel computed tomography perfusion imaging. (A) Patient with an initial right-side tandem occlusion. Left-Panel: Lateral projection of the final DSA imaging showing complete reperfusion without any residual distal vessel occlusions. Middle-Panel: FPCTP imaging showing hypoperfusion in the parieto-occipital region on the contralateral side. Right-Panel: Hypoperfusion findings from immediate FPCTP imaging were confirmed as a subacute infarct on scheduled follow-up imaging. (B) Patient with an initial right-side occlusion of the internal carotid artery. Left-Panel: Lateral projection of the final DSA imaging showing incomplete reperfusion. Middle-Panels: FPCTP image series showing residual perfusion deficit on the frontal right-side. However, there was also hypoperfusion finding on the unaffected left side suggestive of hemodynamic impairment in the borderline zone. Right-Panel: Coronal view of the admission CT imaging showing chronic dissection of the left internal carotid artery near the skull base with high grade stenosis.

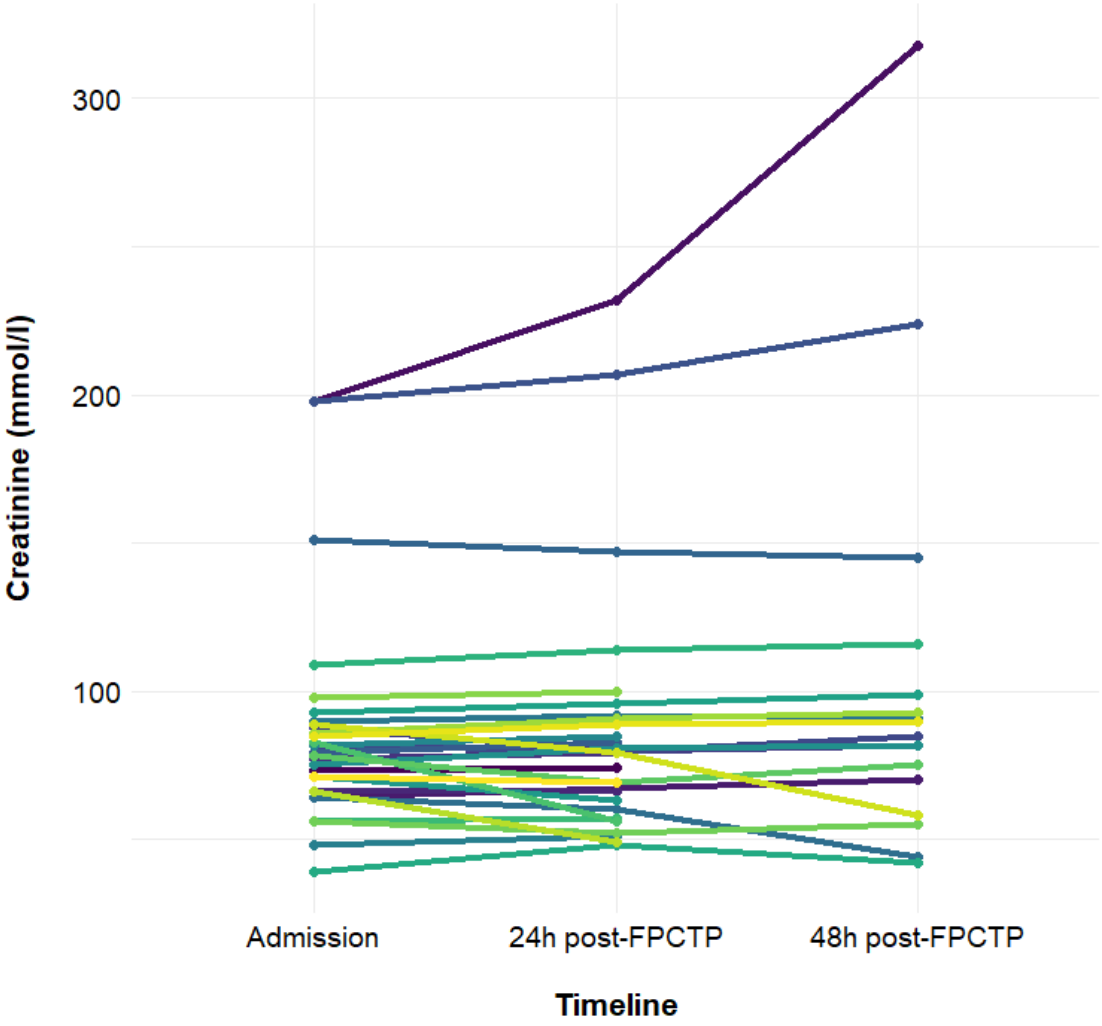
Two patients with contralateral hypoperfusion were classified into Group 1 as DSA and FPCTP showed perfect agreement of in terms of location and size of hypoperfusion in the affected territory (Figure 1D, main manuscript text). A third patient was classified into Group 4 as complete reperfusion in the MT target territory was found on FPCTP despite incompelete reperfusion on the DSA (Figure 2D, main manuscript text). In one of the two cases from Group 1 contralateral hypoperfusion presented as a subacute infarct (Figure S4A, above) and in the other it was a result of a hemodynamic impairment due to a carotid artery dissection (Figure S4B, above). For the third patient with contralateral hypoperfusion (Group 4), we could not find any clear clinical rationale either in baseline or follow-up imaging or in the patient's clinical history, possibly suggesting a FPCTP imaging artifact.

Figure S5 Perfusion Imaging Findings on FPCTP Stratified by Operator TICI grading



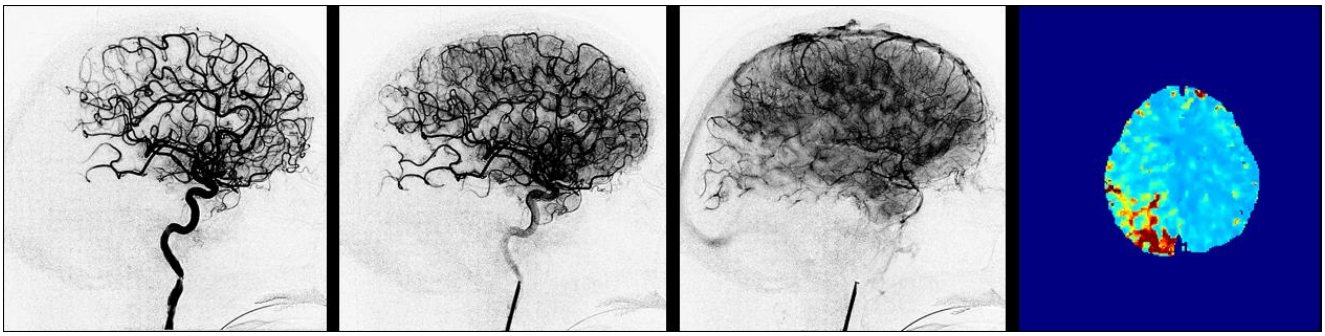
DSA - digital subtraction angiography; FPCTP - flat-panel computed tomography perfusion imaging. When operators have graded reperfusion as incomplete (TICI 2b), perfusion deficits on FPCTP were observed in all patients. Notably also when operator rated reperfusion as complete (TICI 3), perfusion deficits on FPCTP imaging were seen in 75% (n=12/16) cases.

Figure S6 Creatinine Levels



FPCTP - flat-panel computed tomography perfusion imaging. We have found no difference in creatinine levels when comparing values from admission and 24 hours post-FPCTP (p=0.98) or between admission and 48 hours post-FPCTP (p=0.41). Two highest lines represent two patient cases who already had increased creatinine levels on admission due to other comorbidities and it would be difficult to determine if the noted increase was due to the injection of additional contrast related to FPCTP or other medical reasons. Only one patient (top most line in graph) fulfilled the diagnostic criteria for acute kidney injury, as defined in the Contrast Media Safety Committee report.[5]

Figure S7 Persistent Hypoperfusion Without Any Vessel Occlusions



DSA - digital subtraction angiography; FPCTP - flat-panel computed tomography perfusion imaging. Patient with initial right-side M1 occlusion. Lateral projection of the final DSA imaging showing slightly delayed flow, but complete reperfusion without any residual distal vessel occlusions and no clear capillary phase deficit. Findings on immediate FPCTP show hypoperfusion deficit in the parietal region indicating discrepant dichotomized hypoperfusion ratings between the two modalities. Even after reassessment by the core-lab, a residual occlusion could not be identified. Findings could potentially be by no-reflow phenomenon, but this is merely speculative.

REFERENCES

1. Strobel N, Meissner O, Boese J, et al. *3D Imaging with Flat-Detector C-Arm Systems*. Vol 114.; 2009. doi:10.1007/s11547-009-0470-y

2. Manhart MT, Kowarschik M, Fieselmann A, et al. Dynamic iterative reconstruction for interventional 4-D C-Arm CT perfusion imaging. *IEEE Trans Med Imaging*. 2013;32(7):1336-1348. doi:10.1109/TMI.2013.2257178

3. Struffert T, Deuerling-Zheng Y, Kloska S, et al. Dynamic angiography and perfusion imaging using flat detector ct in the angiography suite: A pilot study in patients with acute middle cerebral artery occlusions. *Am J Neuroradiol*. 2015;36(10):1964-1970. doi:10.3174/ajnr.A4383

4. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9):1323-1341. doi:10.1016/j.mri.2012.05.001

5. Morcos SK, Thomsen HS, Webb JAW. Contrast-media-induced nephrotoxicity: A consensus report. *Eur Radiol*. 1999;9(8):1602-1613. doi:10.1007/s003300050894