Appendix for

Quantification of Infarct Core Signal using CT Imaging in Acute Ischemic Stroke

Authors

Uma Maria Lal-Trehan Estrada[1], Grant Meeks[2], Sergio Salazar-Marioni[2], Fabien Scalzo[5], Mudassir Farooqui[4], Juan Vivanco-Suarez[4], Santiago Ortega Gutierrez[4,*], Sunil Sheth[2,3,*], Luca Giancardo[1,3,*]

CONSIDERING ALL PATIENTS OF THE DATASET (n= 88)		**Group-level ideal time (s)**	
Metric used to compute ICS	**Group of patients**	**Median**	**95% CI**
KL	All	3	[1.5, 3]
	<30 mL of infarct core volume	3	[1.5, 3]
	>=30 mL of infarct core volume	3	[1.5, 3]
ED	All	3	[3, 4.5]
	<30 mL of infarct core volume	3	[3, 4.5]
	>=30 mL of infarct core volume	3	[3, 3]
JS	All	3	[3, 3]
	<30 mL of infarct core volume	3	[3, 4.5]
	>=30 mL of infarct core volume	3	[3, 3]

Table A1. *Group-level ideal time and 95% confidence interval retrieved using bootstrap on 90% of the patients with 1000 iterations, based on the Kullback-Leibler divergence (Contralateral R. || Infarct core R.), the Euclidean distance (Infarct core R. || Contralateral R.) and the Jensen-Shannon distance (Infarct core R. || Contralateral R.). Note that the group-level ideal time in all cases is 3 seconds, which means that the ideal CT(A), the one providing highest ICS, corresponds to a scan acquired 3 seconds after the mid arterial phase.*

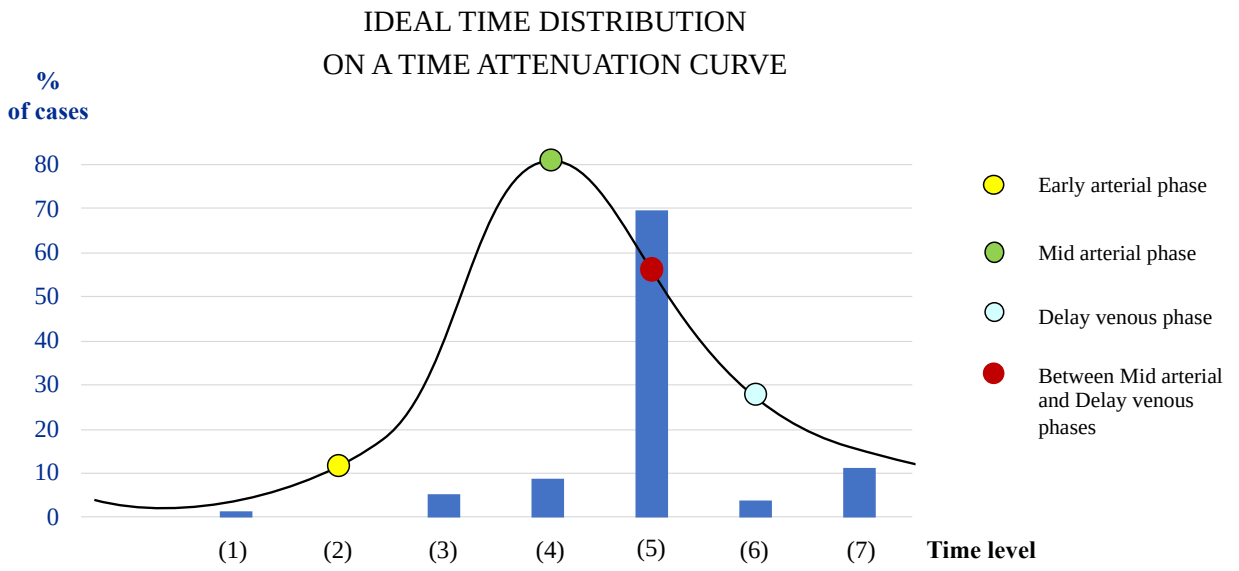


Figure A1. *Percentage of cases providing the highest ICS at 7 different time levels: before the early arterial phase (1.3 %), at the early arterial phase (0 %), between the early and the mid arterial phases (5.1 %), at the mid arterial phase (8.9 %), between the mid and the delayed venous phases (69.6 %), at the delayed venous phase (3.8 %) and after the delayed venous phase (11.4 %). The highest ICS corresponds to the highest Kullback-Leibler divergence between the contralateral region and the infarct core region and for most cases (69.6 %) it is provided by a CTA scan acquired between the mid arterial phase and the delayed venous phase. These percentages are derived from the* ***dataset excluding the patients with intracerebral hemorrhage on the MRI DWI****.*

Excluding patients with intracerebral hemorrhage on the MRI DWI (n = 79)		**Group-level ideal time (s)**	
Metric used to compute ICS	**Group of patients**	**Median**	**95% CI**
KL	All	3	[1.5, 3]
	<30 mL of infarct core volume	3	[1.5, 3]
	>=30 mL of infarct core volume	3	[1.5, 3]
ED	All	3	[3, 4.5]

	<30 mL of infarct core volume	4.5	[3, 4.5]
	>=30 mL of infarct core volume	3	[3, 3]
JS	All	3	[3, 3]
	<30 mL of infarct core volume	3	[3, 4.5]
	>=30 mL of infarct core volume	3	[1.5, 3]
KL MC	All	3	[3, 3]
	<30 mL of infarct core volume	3.75	[3, 4.5]
	>=30 mL of infarct core volume	3	[3, 3]

Table A2. *Group-level ideal time and 95% confidence interval retrieved using bootstrap on 90% of the patients (excluding the patients with intracerebral hemorrhage on the MRI DWI) with 1000 iterations, based on the Kullback-Leibler divergence (Contralateral R. || Infarct core R.), the Euclidean distance (Infarct core R. || Contralateral R.) and the Jensen-Shannon distance (Infarct core R. || Contralateral R.). Note that the group-level ideal time when considering all 79 patients using any of the 3 metrices is 3 seconds, which means that the ideal CT(A), the one providing highest ICS, corresponds to a scan acquired 3 seconds after the mid arterial phase.* ***These values are derived from the dataset excluding the patients with intracerebral hemorrhage on the MRI DWI.***

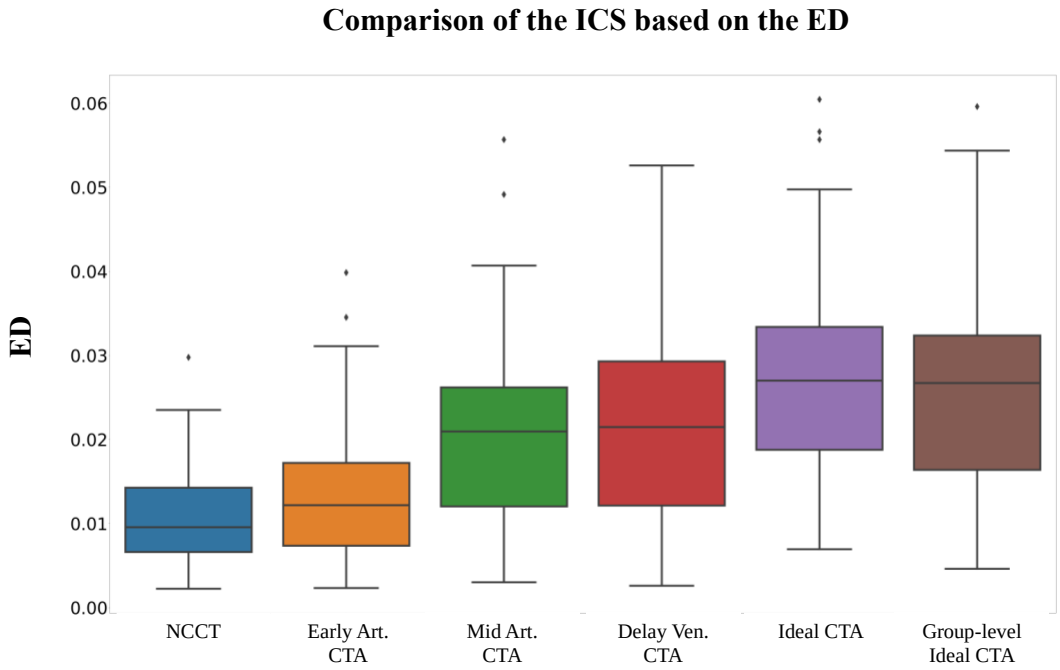


Figure A2. *Boxplots for 6 different scans (NCCT; Early arterial CTA; Mid arterial CTA; Delayed venous CTA; Ideal CT(A); Group-level Ideal CT(A)) representing the distribution over the 88 patients of the Euclidean distance (ED) between the contralateral region and the infarct core region. Ideal CT(A): CTA providing the highest Euclidean distance between the contralateral region and the infarct core region, specific for each patient. Group-level Ideal CT(A): CTA at 3 seconds after the mid arterial phase.*

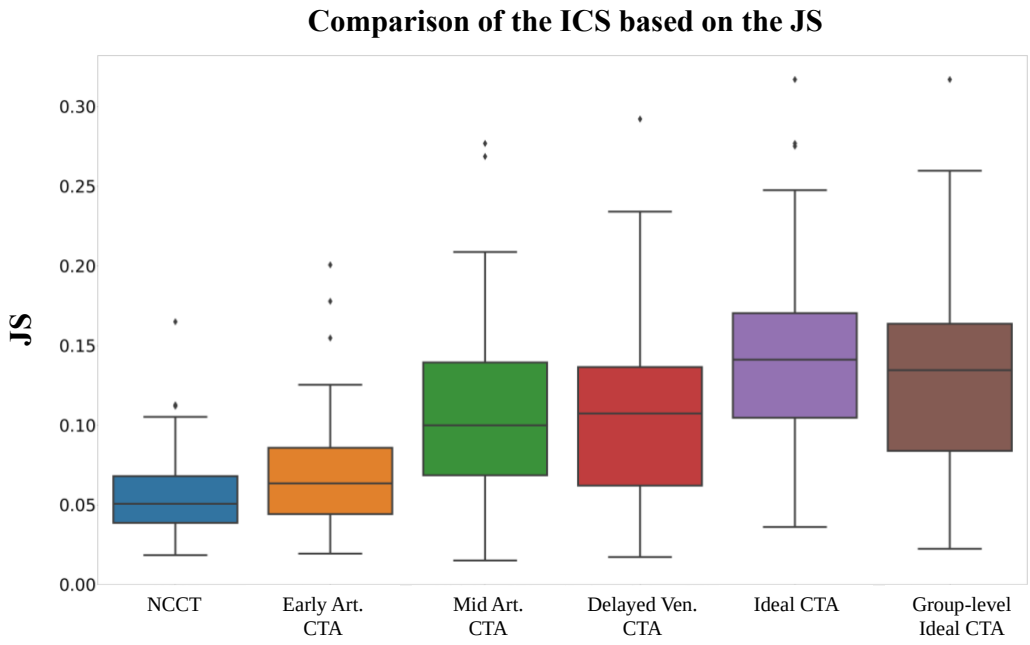


Figure A3. *Boxplots for 6 different scans (NCCT; Early arterial CTA; Mid arterial CTA; Delayed venous CTA; Ideal CT(A); Group-level Ideal CT(A)) representing the distribution over the 88 patients of the Jensen-Shannon distance (JS) between the contralateral region and the infarct core region. Ideal CT(A): CTA providing the highest Jensen-Shannon distance between the contralateral region and the infarct core region, specific for each patient. Group-level Ideal CT(A): CTA at 3 seconds after the mid arterial phase.*

	Metric used to compute ICS					
	ED		**KL**		**JS**	
Infarct core volume (mL)	Mid arterial CTA vs Ideal CTA	Mid arterial CTA vs Group-level Ideal CTA	Mid arterial CTA vs Ideal CTA	Mid arterial CTA vs Group-level Ideal CTA	Mid arterial CTA vs Ideal CTA	Mid arterial CTA vs Group-level Ideal CTA
All volumes	***	*** [***,***]	***	*** [***,***]	***	*** [***,***]
< 30	***	*** [***, ***]	***	** [***, **]	***	*** [***,***]
>= 30	***	*** [*** , **]	***	*** [***, ***]	***	*** [***, ***]

Table A3. *Statistical significance, using Wilcoxon signed-rank test, of the difference of ICS between mid arterial CTAs and Ideal CT(A)s and between mid arterial CTAs and Group-level Ideal CT(A)s for different groups of patients: all volumes (group that considers all patients n=88), < 30 (group that considers patients with infarct core volume smaller than 30 mL, n = 44) and >=30*

(group that considers patients with infarct core volume larger or equal than 30 mL, n = 44). For the comparison with respect to the Group-level Ideal CT(A), we show the significance of the difference when using the median time and the two edges of the 95% confidence interval for each metric. The significance of the difference is shown using the following notation: "-": equal distributions, no comparison performed; "ns" (non-significant): 5E-02 < p <= 1; "": 1E-02 <p <= 5E-02; "**": 1E-03 <p <= 1E-02; "***": p <= 1E-03; where p is the p-value obtained in the statistical test.*

	Dataset excluding haemorrhagic transformation cases change between contralateral region and infarct core region					
	Metric used to compute ICS					
	EUCLIDEAN DISTANCE (ED)		**KULLBACK-LEIBLER DIVERGENCE (KL)**		**JENSEN-SHANNON DISTANCE (JS)**	
	Median [interquartile range]	Median difference and Statistical significance of Difference w.r.t Mid Arterial Phase / Difference w.r.t Group-level Ideal Phase	**Median [interquartile range]**	Median difference and Statistical significance of Difference w.r.t Mid Arterial Phase / Difference w.r.t Group-level Ideal Phase	**Median [interquartile range]**	Median difference and Statistical significance of Difference w.r.t Mid Arterial Phase / Difference w.r.t Group-level Ideal Phase
NCCT	0.009 [0.007 – 0.015]	(-0.012) *** / (-0.017) ***	0.008 [-0.002 – 0.016]	(-0.034) *** / (-0.068) ***	0.053 [0.040 – 0.070]	(-0.056) *** / (-0.086) ***
EARLY ARTERIAL CTA	0.013 [0.008 – 0.017]	(-0.008) *** / (-0.014) ***	0.013 [0.005 – 0.024]	(-0.029) *** / (-0.063) ***	0.064 [0.047 – 0.086]	(-0.044) *** / (-0.074) ***
MID ARTERIAL CTA	0.021 [0.012 – 0.027]	- / (-0.005) ***	0.042 [0.015 – 0.097]	- / (-0.034) ***	0.108 [0.066 – 0.141]	- / (-0.030) ***
DELAYED VENOUS CTA	0.022 [0.012 – 0.029]	(0.001) ns / (-0.005) ***	0.041 [0.014 – 0.081]	(-0.002) ns / (-0.036) ***	0.110 [0.062 – 0.139]	(0.002) ns / (-0.028) ***

IDEAL CT(A)	0.027 [0.018 – 0.035]	(0.006) *** / (0.000) ***	0.084 [0.037 – 0.150]	(0.042) *** / (0.008) ***	0.142 [0.104 – 0.173]	(0.033) *** / (0.003) ***
GROUP-LEVEL IDEAL CT(A)	0.027 [0.016 –0.032]	(0.005) *** / -	0.076 [0.027 – 0.140]	(0.034) *** / -	0.134 [0.084 – 0.164]	(0.030) *** / -

Table A4. *Median and interquartile range of the ICS measured using 3 metrices (Euclidean distance, Kullback-Leibler divergence and Jensen-Shannon distance), for 6 scan types (non-contrast CT, Early arterial CTA, Mid arterial CTA, Delayed venous CTA, Ideal CT(A) and Group-level Ideal CT(A)). Higher values of the metrices correspond to higher ICS. The Ideal CT(A) is different for each metric; it corresponds to the CTA providing the highest value of the metric. The Group-level Ideal CT(A) is the scan acquired at the group-level ideal time, that is, 3 seconds after the mid arterial phase. The distribution of the metric values for each CTA is compared to the metric values obtained for the Mid arterial CTA and the Group-level Ideal CT(A). The significance of the difference tested using Wilcoxon signed-rank test is shown using the following notation: "-": equal distributions, no comparison performed; "ns" (non-significant): 5E-02 < p <= 1; "*": 1E-02 <p <= 5E-02; "**": 1E-03 <p <= 1E-02; "***": p <= 1E-03; where p is the p-value obtained in the statistical test. These results are derived from the* ***dataset excluding the patients with intracerebral hemorrhage on the MRI DWI.***

ADDITIONAL FIGURES / TABLES

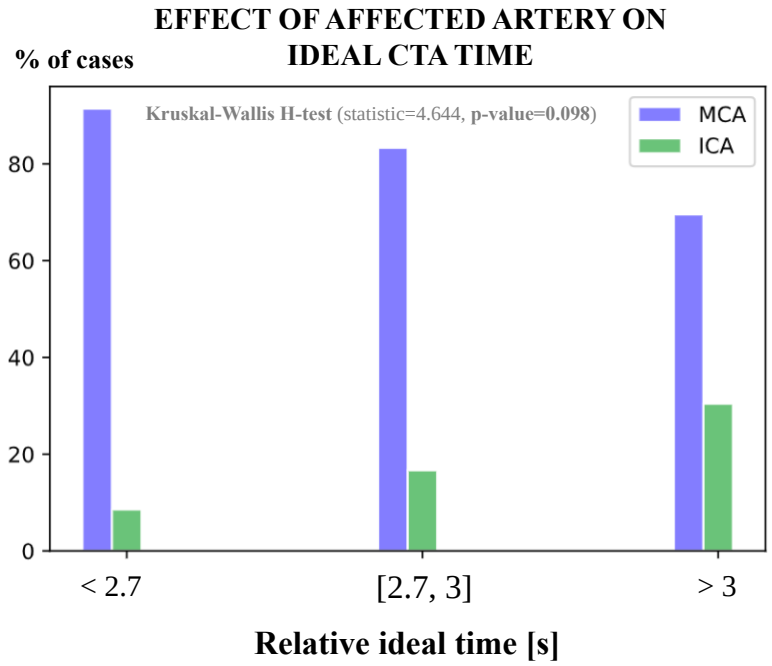
DETERMINANTS OF CHANGES IN THE IDEAL CT(A):

Additional secondary endpoints included determinants of changes in the ideal time, including time from stroke onset to imaging as well as occlusion location. For the occlusion location variable, patients were split into tertiles based on their ideal time, and the analysis was performed using Kruskal-Wallis H-test. As for the time from stroke onset to imaging, the correlation with the ideal time was calculated.

Regarding the last known well (LKW) time, a significant spearman correlation with a coefficient of -0.23 was found with respect to the ideal time relative to the mid arterial phase time. Specifically, a higher time from stroke onset to imaging was associated to a lower relative ideal time (closer to or even before the mid arterial phase).

Based on the values of the relative ideal time, 3 groups of patients were identified. Quantiles 40% and 60 %, corresponding to 2.7 seconds and 3 seconds, were chosen so as to have groups with a comparable number of patients (Group 1 (<2.7 s): 35 patients; Group 2 ([2.7, 3] s): 30 patients; Group 3 (>3 s): 23 patients).

For each group of patients, the percentage of cases having the middle cerebral artery (MCA) affected and the internal carotid artery (ICA) affected can be seen in the Figure below:



Occlusion location (middle cerebral artery, MCA, or internal carotid artery, ICA) for each of the 3 groups based on the relative ideal time. Kruskal-Wallis H-test of the difference among these 3 groups. Although not significant, an occlusion located on the

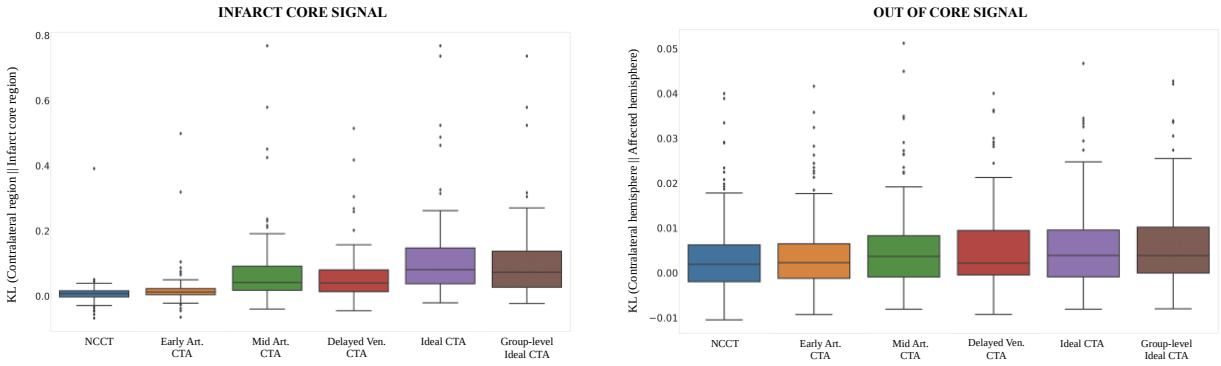
MCA seems to be associated with a lower relative time; while an occlusion located on the ICA seems to be associated to a higher relative ideal time.

Although not significant based on the Kruskal-Wallis H-test (p-value = 0.098), cases with affected MCA tend to have a lower relative ideal time (ideal time closer or before the mid arterial phase), while cases with affected ICA tend to have a higher relative ideal time (ideal time after the mid arterial phase).

ICS vs OCS:

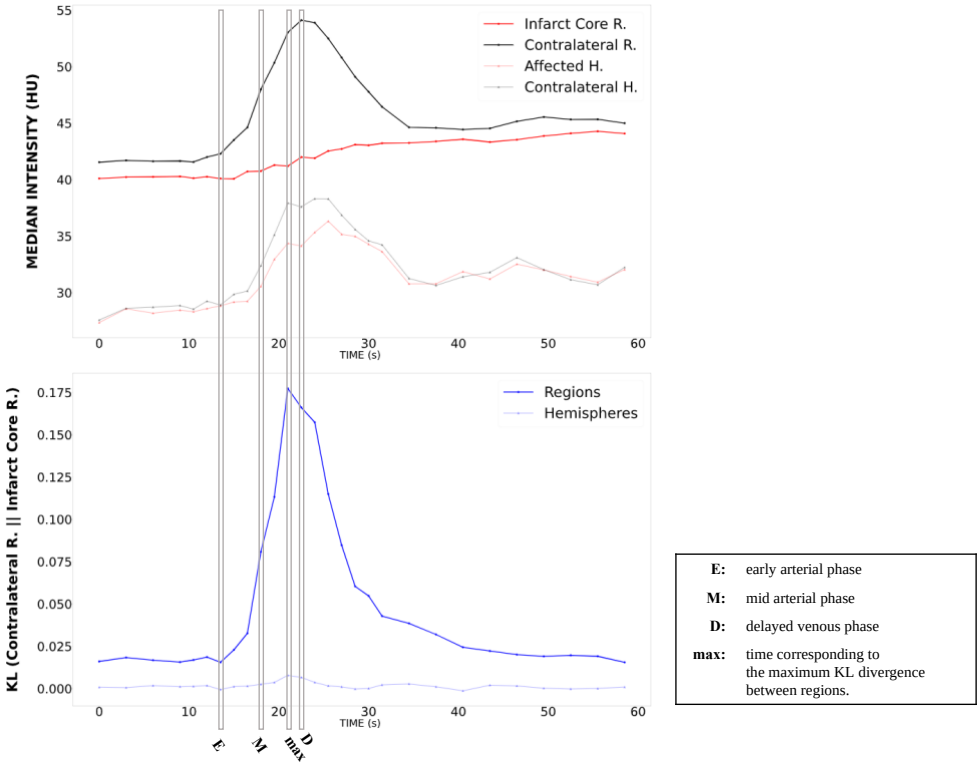
	Mann-Whitney U test significance of ICS vs OCS using:		
	ED	KL (Contralateral R. || Infarct core R.)	JS
NCCT	***	*	***
Early arterial CTA	***	***	***
Mid arterial CTA	***	***	***
Delayed venous CTA	***	***	***
Ideal CT(A)	***	***	***
Group-level ideal CT(A)	***	***	***

Significance of the difference between the ICS and the OCS for each CT scan when using the ED, KL and JS metrices to estimate these signals. The ICS is significantly higher than the OCS in all cases. Note this is remarkable since, therefore, using any of these metrices, the infarct core region can be distinguished from the rest of the hemisphere. The significance of the difference is shown using the following notation: "-": equal distributions, no comparison performed; "ns" (non-significant): 5E-02 < p <= 1; "": 1E-02 <p <= 5E-02; "**": 1E-03 <p <= 1E-02; "***": p <= 1E-03; where p is the p-value obtained in the statistical test.*



Boxplots of the ICS (on the left) and the OCS (on the right) estimated by the KL divergence for 6 different CT(A)s: NCCT, Eartly arterial CTA, Mid arterial CTA, Delayed Venous CTA, Ideal CT(A) and Group-level CT(A). Note that the figures have a different y axis scale as the OCS data is much lower compared to ICS.

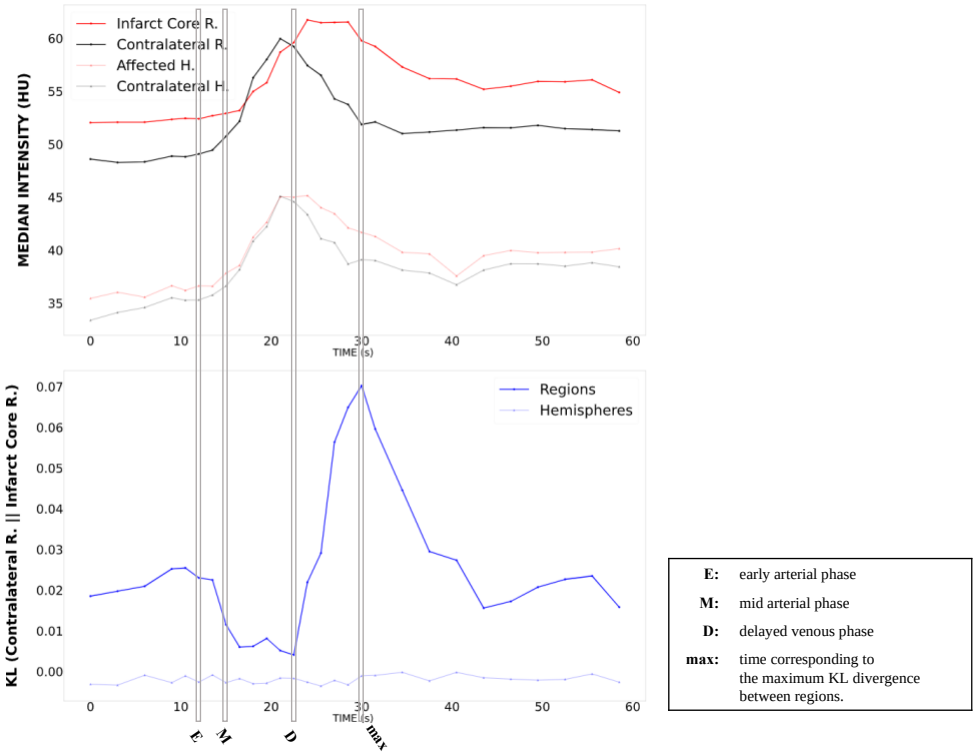
Example ideal time between mid arterial phase and delayed venous phase:



For each scan of the CTP-SI of 1 patient of the dataset: Median intensity in Hounsfield units (HU) of the infarct core region (in red), the contralateral region (in black), the affected hemisphere (light red) and the contralateral hemisphere (light gray); Kullback-Leibler divergence (contralateral region || infarct core region) in blue and Kullback-Leibler divergence (contralateral

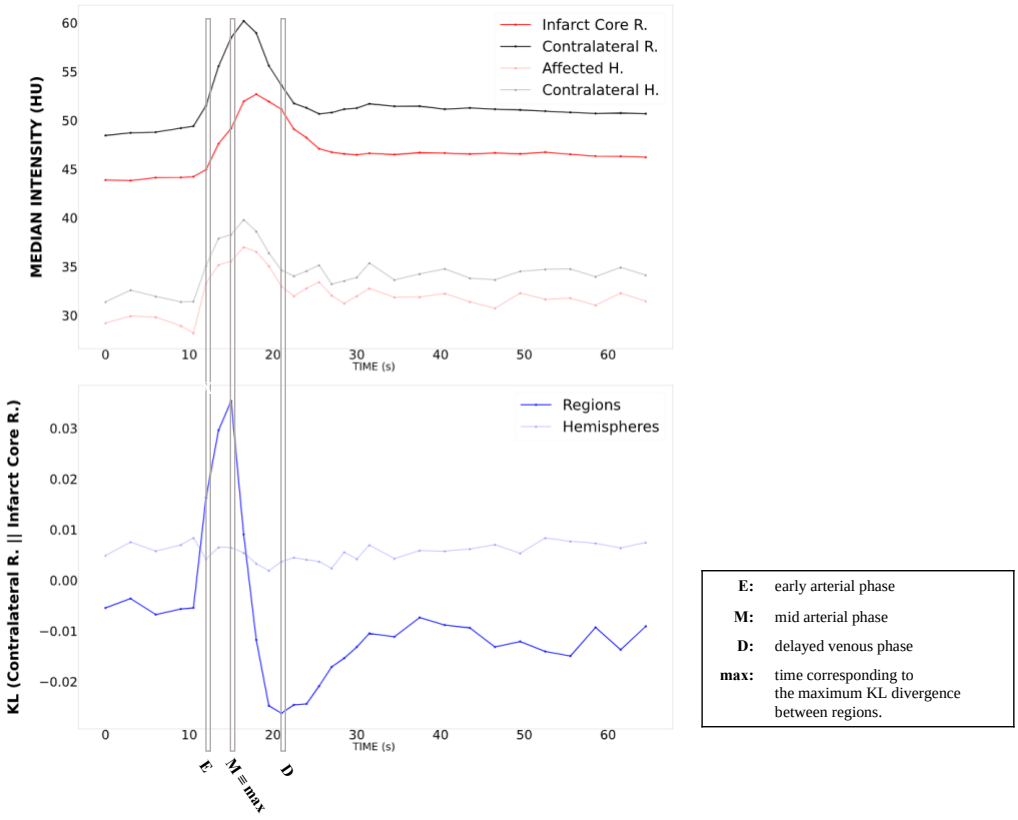
hemisphere || affected hemisphere) in light blue. Note that for this patient, the maximum KL (max) is provided by a scan between the mid arterial phase (M) and the delayed venous phase (D), as in 69.3% of the cases.

Example ideal time after delayed venous phase:



For each scan of the CTP-SI of 1 patient of the dataset: Median intensity in Hounsfield units (HU) of the infarct core region (in red), the contralateral region (in black), the affected hemisphere (light red) and the contralateral hemisphere (light gray); Kullback-Leibler divergence (contralateral region || infarct core region) in blue and Kullback-Leibler divergence (contralateral hemisphere || affected hemisphere) in light blue. Note that for this patient, the maximum KL (max) is provided by a scan acquired after the delayed venous phase (D), as in 10.2 % of the cases.

Example ideal time equal to mid arterial phase:



For each scan of the CTP-SI of 1 patient of the dataset: Median intensity in Hounsfield units (HU) of the infarct core region (in red), the contralateral region (in black), the affected hemisphere (light red) and the contralateral hemisphere (light gray); Kullback-Leibler divergence (contralateral region || infarct core region) in blue and Kullback-Leibler divergence (contralateral hemisphere || affected hemisphere) in light blue. Note that for this patient, the maximum KL (max) is provided by a scan acquired at the mid arterial phase (M ≡ max), as in 9.1 % of the cases.

Dataset information when excluding patients with intracerebral hemorrhage on the MRI DWI:

VARIABLES	**Number (%) of cases (Total of 79 patients)** No patients with intracerebral haemorrhage on the MRI DWI

AGE	**< 20**	0 (0.00 %)
	>= 20 < 40	4 (5.06 %)
	>= 40 < 60	17 (21.52 %)
	>= 60 < 80	**39 (49.37 %)**
	>= 80	19 (24.05 %)
SEX	**F**	**41 (51.90 %)**
ISCHEMIC INFARCT CORE VOLUME ON MRI DWI SEGMENTATIONS (mL)	**< 30**	**40 (50.63 %)**
	>= 30 < 50	14 (17.72 %)
	>= 50 < 70	7 (8.86 %)
	>= 70	18 (22.78 %)
AFFECTED ARTERY	**ICA**	15 (18.99 %)
	MCA	**64 (81.01 %)**
AFFECTED SEGMENT	**ICA CERVICAL**	1 (1.27 %)
	ICA T	12 (15.19 %)
	MCA M1	**44 (55.70 %)**
	MCA M2	20 (25.32 %)
	MCA M3	2 (2.53 %)
TICI SCORE	**GRADE 2B**	**41 (51.90 %)**
	GRADE 2C	9 (11.39 %)
	GRADE 3	29 (36.71 %)

Description of the dataset excluding the patients with intracerebral hemorrhage on the MRI DWI: patient age, patient sex (F: female), ischemic core volume, affected artery (ICA: internal carotid artery; MCA: middle cerebral artery), affected segment, and TICI (thrombolysis in cerebral infarction) score. In bold, the most frequent category for each variable. The ischemic infarct core median volume is 30.63 mL. Note that all patients had a successful recanalization (TICI score >= Grade 2B).

	MEAN TIME (h)	**MEDIAN TIME (h)**
CTP TIME - LKW TIME	6.98	4.07 [2.98 – 7.96]

MRI TIME - REPERFUSION TIME	20.78	19.88 [8.50 – 23.47]

Time difference between the CTP-SI acquisition and the last known well time (CTP-SI TIME - LKW TIME), that is, time from stroke onset to imaging, and time difference between the MRI acquisition and the reperfusion therapy (MRI TIME – REPERFUSION TIME). The CTP-SI median acquisition time was approximately 4 hours after the LKW. The MRI median acquisition time was approximately 20 hours after the therapy. Information derived from the dataset excluding the patients with intracerebral hemorrhage on the MRI DWI.