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Title: What is the relationship among penumbra volume, collaterals and time since onset in the first 6h after acute ischemic stroke?

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Abstract:

Background: The steep, time-dependent loss of benefit from reperfusion in clinical trials is consistent with loss of penumbra over the early hours of ischaemia, as observed in animal models. Human imaging studies, however, show persistent penumbra for up to 48h. We investigated core and penumbra volumes and collateral status in relation to time after stroke onset within the first 6h.

Methods: Using data from three multimodal CT-based studies in acute ischaemic stroke patients <6h after onset, we measured core and penumbra volumes, collateral status, and target mismatch (defined as core volume<50ml, perfusion lesion volume>15ml, mismatch ratio>1.8). Patients were grouped by onset to imaging time (<3, 3-4.5, 4.5-6h). We explored correlates of penumbra proportion by multivariable linear regression.

Results: Analysis included 144 subjects. Across time epochs, neither proportions of penumbra (59%, 64%, 75% at <3, 3-4.5, >4.5h respectively, $p=0.4$) nor poor collaterals (15/56 (27%), 14/47 (30%), 4/15 (27%) at <3, 3-4.5, >4.5h, $p=0.9$) differed significantly. Penumbra proportion was not clearly related to time to imaging ($R^2=0.003$; $P=0.5$) but a trend for divergent effects by collateral status was seen (slight increase in penumbra over time with good collaterals versus reduced with poor, interaction $p=0.08$). The proportion of patients with target mismatch did not vary by time (56%, 74%, and 67% at <3, 3-4.5, >4.5h; $p=0.09$).

Conclusions: In a cross-sectional sample imaged within 6h, neither the proportions of penumbral tissue nor “target mismatch” varied by time from onset. A trend for reducing penumbra proportion only among those with poor collaterals may have pathophysiological and therapeutic importance.

Introduction:

The concept of the ischaemic penumbra segregates ischaemic brain tissue according to flow thresholds, penumbra being the tissue below the threshold for electrical failure, but above the threshold for energy failure and loss of neuronal integrity, which define ischaemic core (1, 2). Conventionally, core is believed to grow over time at the expense of penumbra, and is understood to be a consequence of the dynamic interaction of multiple factors including peri-infarct spreading depressions and adverse neurochemical events (3). In animal models, transient MCA occlusion for 2-3 hours results in moderate to large infarct sizes reaching that of permanent MCA occlusion(4, 5), while on PET(6) and multi parametric imaging of protein and ATP synthesis(7), penumbra was almost absent 6-8 hours after permanent MCA occlusion .

Consistent with animal data on penumbra decline, the probability of favourable clinical outcome declines rapidly with increasing onset-to-treatment or onset-to-reperfusion time for both IV Thrombolysis (8) and endovascular reperfusion(9) within the first 6-8 hours after symptom onset. Although unproven, the concept of “collateral failure” and consequent penumbral loss as a function of duration of ischaemia has been suggested as a possible explanatory factor for this time dependence (10).

Clinical imaging observations are, however, not uniformly consistent with this explanation. Several human studies show persistence of imaging features accepted as consistent with penumbra for much longer across modalities including PET(11) , MRI perfusion-diffusion mismatch (12) and for time periods of up to 48h. Using Xenon CT within 6 hours of MCA occlusion, penumbra represented a constant proportion of MCA territory ($32\pm 7\%$; range,

16.2% to 46.9%) while the proportion of core showed wide inter-individual variation (37.6%±18.7%; range, 7.6% to 70.5%), (13). In proximal arterial occlusion, good collaterals were associated with both favourable tissue and clinical outcomes, while time from onset was unrelated to either collateral grade or mismatch proportion (14). In patients treated with endovascular therapy, the interaction of good collaterals and reperfusion, but not time from symptom onset to reperfusion, influenced penumbral tissue loss (15).

We investigated the relationship of penumbra volume, collateral status and their interaction over time within 6 hours of stroke onset.

Methods: Subjects were recruited at a single centre for one of three multimodal imaging studies undertaken between 2008 and 2013(16, 17). Two were observational studies and one was a clinical trial comparing two thrombolytic agents. In the two observational studies (one investigating feasibility of complex imaging, one investigating pathophysiology of acute hyperglycaemia), all ischemic stroke patients aged above 18 years and presenting up to 6 hours after symptom onset were eligible. In the clinical trial, patients eligible for thrombolysis within 4.5 hrs were randomised to receive either alteplase or tenecteplase. Patients were excluded if they had contraindications to contrast administration (history of allergy or estimated Glomerular Filtration Rate <30ml/min). In all studies, acute ischaemic stroke patients underwent non-contrast CT (NCCT), CT angiography (CTA) and CT perfusion (CTP) imaging at baseline (<6h after onset) with follow-up brain imaging with CT at approximately 24h after recruitment, and repeat CTA if occlusion was present on baseline imaging. Clinical outcome was evaluated at 30 days or 3 months.

For this analysis, we selected subjects with a perfusion lesion and anterior territory arterial occlusion (ICA, M1, M2, or M3).

Imaging acquisition:

All scans were performed on a Philips Brilliance 64 multidetector scanner. Whole brain NCCT was acquired first, (5 mm slice thickness FOV 218 x 218 mm, 120 kv, 171 mA or 0.9 mm slice thickness, FOV 250x250 mm, 120 kV, 404 mA) followed by CTP with 40 mm slab coverage from the basal ganglia (8x5 mm slices, FOV 25 cm, 80 kVp, 476 mA, 2 second cycle time, 30 cycles) using a 50 ml contrast bolus administered at 5 mls per second (350 Xenetix) via a large-gauge cannula. A CTA covering aortic arch to the top of the lateral ventricles (0.67 mm slice thickness, 120 kV, 475 mA) was acquired during the first arterial

past of contrast (Xenetix 350, 60 ml, followed by 30 ml of saline bolus, both given at 5 ml per second).

Imaging processing and analysis:

Imaging studies were anonymised, and analysed independently by two research fellows (BC, XH). CT perfusion was processed offline using MiStar (Apollo Medical Imaging Technology, Melbourne, Australia). Deconvolution of tissue enhancement curves and arterial input function (AIF) selected from the anterior cerebral artery was performed using modified singular value decomposition (SVD) with compensation for the effects of arterial delay and dispersion. Delay time (DT) was determined by a delay corrected SVD deconvolution by applying a series of delay time (DT) values, with actual delay time being minimum DT value, which produces $T_{max}=0(18)$. Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV) were calculated from the peak height and area under tissue enhancement curves respectively, and Mean Transit Time (MTT) = CBV/CBF .

Penumbra definitions:

Ischaemic core was defined as tissue with reduced CBF (relative CBF <40% of contralesional hemisphere) and prolonged delay time (relative DT >2 sec); penumbra volume was defined as tissue with relative DT >2 sec but relative CBF \geq 40% of contralateral (19). We used Relative penumbral volume (% , penumbra volume/ total ischemic lesion volume) \times 100) throughout this paper.

Collateral scores:

If retrograde flow was seen on CTP, collaterals were graded on CTA qualitatively (14). We defined collaterals as good (angiographic flow distal to occlusion), moderate (angiographic flow to ischemic territory but not distal to occlusion), or poor (contrast opacification only in distal superficial branches). We used a modified Miteff's classification to incorporate terminal ICA, M1 and M2 occlusion, whereas the original classification excluded M2 occlusion (14).

Target mismatch:

Target mismatch was defined as a perfusion lesion >15 ml with core volume < 50 ml and mismatch between perfusion lesion and core $>1.8(20)$. To account for the limited z axis coverage of CTP, we reduced the 70ml threshold used by EXTEND-IA(21) and DEFUSE-2(20) proportionately, by dividing the mean of (Coregistered Infarct volume over 4cm/Total Infarct volume from whole brain NCCT) in the non-recanalised group. This figure was 0.7 (i.e. Approximately 70% of total infarct is in the 4 cm slab covered by CTP). This was multiplied by 70ml, to yield an adjusted volume of 50ml to define target mismatch.

Statistical analysis:

We compared the groups across 3 time epochs: <180 , 180-270, and >270 min from stroke symptom onset to CTP acquisition time. We used chi-square or Fisher's tests for categorical variables and Mann-Whitney tests for continuous variables. We conducted linear regression for the prediction of penumbra proportion. We used IBM SPSS Statistics 22 version for all the statistical analysis.

Results:

From a total of 263 subjects, 180 had a visible perfusion lesion on perfusion imaging, 147 of whom had anterior territory occlusion (ICA=40, M1=60, M2= 39, M3= 8); CTP was available in 144 subjects, who constituted the main analysis population. Collateral assessment was possible in 118 with retrograde flow on CTP-SI, who constituted the population analysed for relationship to collaterals (Figure 1). 28 patients with anterograde flow distally from occlusion were excluded from collateral grading as they would not represent true collateral circulation. In the main analysis group, the overall population had median age 74 years (IQR 63-81) and median NIHSS 15(10-20). On initial imaging, median ASPECT score was 7 (5-9), median core volume 23ml (IQR 11-48), and median penumbra volume 42 ml (IQR 25-65). Occlusion was present in the ICA (or tandem) in 39 (27%), MCA M1 segment in 59 (41%), M2 in 38 (26%), and M3 in 8 (5%). Baseline characteristics in the subgroup of 118 with assessable collateral status did not differ from the overall study population.

Baseline clinical and imaging characteristics across time epochs (<3, 3-4.5, >4.5 h) are detailed in Table 1. There were no significant differences in baseline characteristics. Across time epochs, neither relative penumbra volume (59%, 64%, 75% at <3, 3-4.5, >4.5h respectively, $p=0.4$; Figure 2), absolute penumbra volumes (41(22-58), 46 (32-69), 40 (26-76) at <3, 3-4.5, >4.5 h respectively, $p=0.3$; Figure 2), target mismatch (56%, 74%, 67% at <3, 3-4.5, >4.5 h respectively, $p=0.09$; Figure 2), nor poor collaterals (15/56 (27%), 14/47 (30%), 4/15 (27%) at <3, 3-4.5, >4.5h, $p=0.9$; Figure 2) differed significantly.

Median penumbra proportion was 45% with poor collaterals versus 72% with good or moderate collaterals ($P<0.001$); relative penumbra volume was not clearly related to time to

imaging ($R^2=0.003$, $p=0.5$; Figure 3) but a trend for divergent effects by collateral status was seen (slight increase in penumbra over time with good or moderate collaterals versus reduced with poor, $R^2=0.03$ for both; $p=0.08$; Figure 3). In univariate linear regression, potentially significant variables predicting proportion of relative penumbra volume ($p < 0.1$) were: large artery (ICA or M1) occlusion, good or moderate collaterals, time to CTP*good or moderate v poor collaterals, diabetes and NIHSS. Age, time to CTP, systolic blood pressure and blood glucose were not significant predictors of Penumbra proportion (Table 2). In multivariate linear regression, NIHSS, good or moderate collaterals versus poor collaterals remained independently significant predictors of penumbra proportion (Table 3).

We analysed a sub-group of ICA and M1 occlusion patients ($n=100$) to explore whether the lack of variability in penumbra proportion also holds true in a more homogeneous group.

Relative penumbra volume was not clearly related to time to imaging ($R^2=0.009$; $p=0.3$. supplementary data figure I), but a trend for divergent effects by collateral status was again seen (slight increase in penumbra over time with good collaterals versus reduced with moderate or poor, $R^2=0.04$ for both; $p=0.09$. Supplementary data figure II).

Discussion:

Our findings in this cross-sectional study population are consistent with previous reports showing persistence of an imaging-defined penumbra in humans, with no evidence of penumbral decline that could explain the time-dependence of therapeutic benefit from reperfusion therapy within the first 6h after stroke onset(13). This was the case regardless of whether penumbra was assessed by absolute volume, volume relative to core, the proportion

of patients with “target mismatch”, or the presence of favourable collateral flow patterns. The sustained presence of penumbra on imaging in human studies contradicts the assumption that the short effective time window for clinical benefit from reperfusion can be explained by steep, time dependent, penumbral decline within first few hours from onset as observed in animal models(1, 9, 22).

Our main observation of interest was a potential divergent effect of penumbral proportion over time according to collateral status, with lower proportions of penumbra in later times being seen only among those with poor collateral flow. This observation challenges the concept of “collateral failure” as a general mechanism driving the loss of penumbral tissue over time (10), and instead suggests that the collateral status at initial presentation may define a group with a different natural history and much shorter time to intervene. A larger study will be needed to investigate these further (In our study, the results suggest a trend with a p value =0.08). These observations are consistent with previous studies. Bang and colleagues (23) studied the interaction of collaterals and perfusion-diffusion mismatch (perfusion lesion defined as $T_{max} \geq 4$ s) and found that neither collateral grading, nor mismatch lesion volumes correlated with time. Poor collaterals were independently correlated with larger infarct growth. Jung and colleagues, in 44 subjects with M1 or M2 occlusion undergoing endovascular therapy within 6 hours and resulting in at least partial reperfusion, showed that elapsed time accounted for only a minor proportion of penumbra tissue (defined as $T_{max} \geq 6$ s) loss in good collateral grades but a larger proportion in poor collateral grades (15).

A wide variety of methods for collateral assessment have been proposed,(24) and only limited study of the consistency of these competing approaches has been undertaken. The

approach used here, modified from that of Miteff,(14) requires time-resolved vessel imaging, and may be closer to the multiphase CTA approach developed by Goyal and colleagues and deployed in the majority of patients recruited to the ESCAPE trial (25). Whether single-phase CTA would yield equivalent findings in clinical use is unclear, and in addition, all of these collateral assessment methods are confined to occlusions of the terminal ICA or proximal MCA. Validation using other methods of collateral assessment and in other vascular territories will be important.

Our conclusions are limited by the limited number of subjects, particularly after 4.5 hours from symptom onset, and the limited range of onset-to-imaging times that were covered in our dataset. To our knowledge, this is the first CT perfusion study assessing the association of penumbra volume with time and our patient cohort is larger than MRI based studies reported previously (15). Since CTP has important practical advantages over MRI, it has become more widely used in patient selection protocols, especially for recent endovascular trials, and characterisation of the relationships between perfusion characteristics and collaterals for this modality are therefore important. We used validated thresholds (18, 26) for core and penumbra, but thresholds for CT perfusion are not uniform, and their derivation is based on limited numbers(27). In common with the majority of imaging studies, we have to infer the persistence of a presumed time-dependent imaging appearance from cross-sectional data rather than sequential imaging in each patient. Repeated imaging studies in the acute stroke population are logistically extremely difficult since patient care may be compromised, and in addition, radiation and contrast exposure limit the repeatability of CTP. Our CT scanner had restricted brain parenchyma coverage of 4 cm on a single acquisition, requiring us to modify the definitions of “target mismatch” based on whole brain volumes in large detector CTP(21) or MRI studies for this more restricted brain coverage, but the 50ml core volume criterion,

while obtained by the ratio of 4cm coverage volume to whole brain volume, has not been validated independently. It is possible that larger volume acquisition, either by undertaking two examinations for contiguous 4cm slabs, or with larger detector scanners, might disclose a different relationship from that demonstrated here, since this may improve coverage of anatomically marginal brain regions omitted by a protocol centred predominantly on the basal ganglia. It is also possible that the limited time period covered may disguise relationships between collaterals and penumbra that become evident over longer observation periods(10). Our purpose, however, was to explore the potential relevance of these MRI-defined phenomena over the time scale relevant to early intravenous or endovascular therapy.

In conclusion, we found no decrease in the proportion of CTP-defined penumbral perfusion within perfusion lesions, or the proportion of patients with target mismatch or favourable collateral patterns within the first 6 hours after stroke onset. A decline in proportion of penumbra with time was restricted to those with poor collateral status. It is therefore possible that collateral flow grade, rather than time since onset, might define suitability for reperfusion therapies. This may be relevant in identifying patients from unknown onset, wakeup stroke population for thrombolysis. Given the strong effect of time on outcomes after reperfusion treatment, further investigations into the interaction between collaterals, penumbra and time is required

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Disclosures: None

Author's contributions: BC, KM contributed to study design, data interpretation, literature search, writing. BC contributed to data analysis. XH contributed to data collection, data analysis, writing. FM contributed to data collection, data interpretation and writing.

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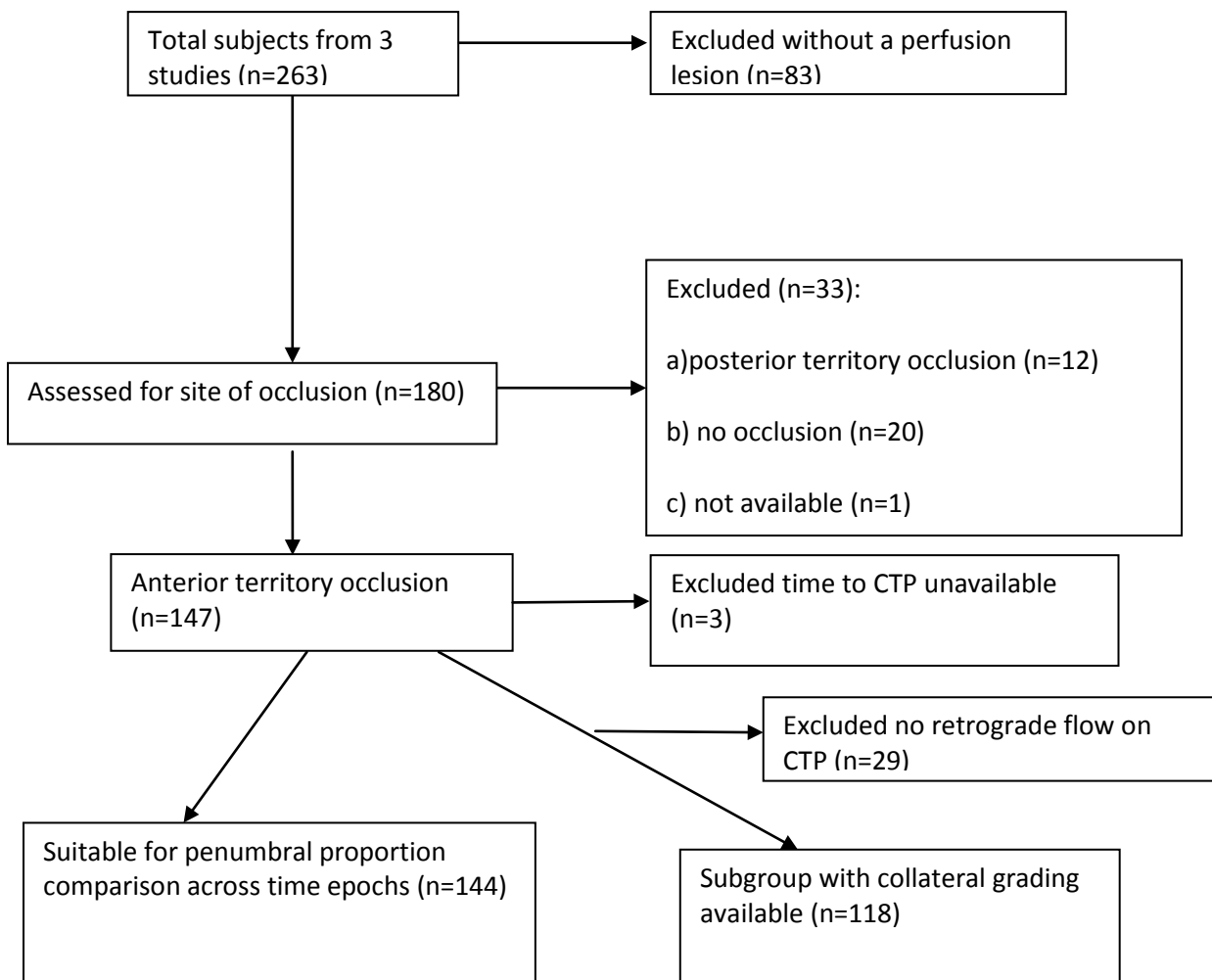


Figure1. Study CONSORT chart

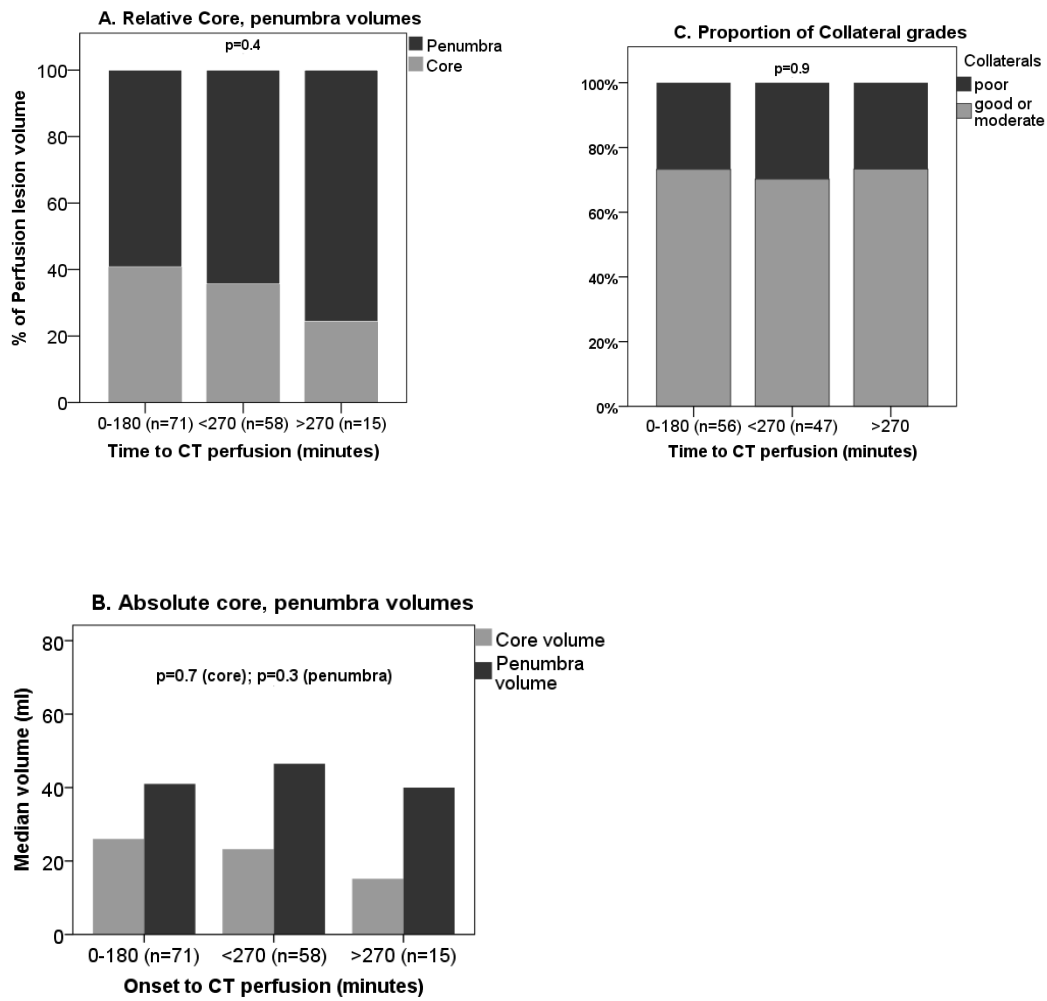


Figure 2. Relative (Panel A), absolute (Panel B) Core, penumbra volumes and collateral grades (Panel C) across time epochs.

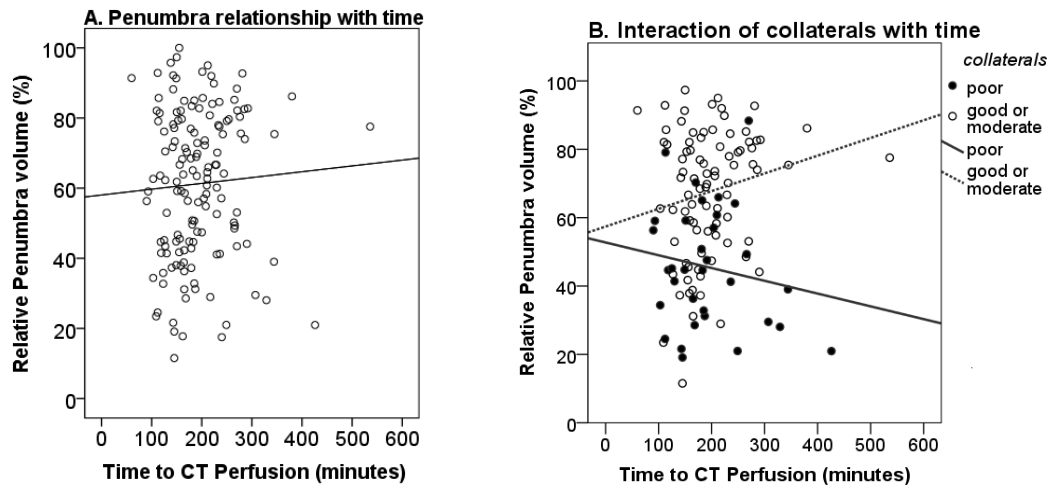


Figure.3. Penumbra relationship with time alone (Panel A) & interaction of collaterals with time (Panel B).

Table1. Baseline characteristics of study population (n=144)

	Time to CT Perfusion (in minutes)			
	0-180 min(n=71)	181-270 min(n=58)	>270min(n=15)	p value
Female (n, %)	28 (39.4%)	32 (55%)	5 (33%)	0.1
Right side ischemia (n, %)	32(46%)	32 (55%)	7 (47%)	0.55
Age, years (median, IQR)	72(62-79)	76(70-81)	71(61-80)	0.053
NIHSS (median, IQR)	16(9-21)	14(10-19)	14.5(6.75-19)	0.34
ASPECT score (median, IQR)	7(5-9)	7(5-9)	6(5-7)	0.6
ASPECT score 0-4	11(15%)	11(19%)	1(7%)	0.1
ASPECT score 5-7	35(48%)	20(35%)	11(73%)	
ASPECT score 8-10	26(36%)	27(47%)	3(20%)	
Glucose (mmol/l)(median, IQR)	6.6(5.7-8.2)	6.8(5.6-8.2)	5.9(5.3-6.7)	0.3
Systolic Blood Pressure mmHg (median, IQR)	143(135-162)	149(137-171)	142(131-160)	0.5
Previous Stroke or TIA (n,%)	12/71(17%)	17/57(30%)	3/14(21.4%)	0.22
Atrial fibrillation (n, %)	29 (42%)	25 (47%)	3 (21%)	0.22
Diabetes	9 (13%)	6 (10%)	1(6.7%)	0.77
Hypertension (n, %)	43 (61%)	34 (58.6%)	8 (53%)	0.8
Hyperlipidemia (n, %)	36 (51%)	29 (50%)	9 (60%)	0.77
Site of vessel occlusion				
ICA/tandem occlusion (n, %)	19 (27%)	16 (27.6%)	4 (26/7%)	0.9
M1 (n, %) *	26 (36.6%)	26 (45%)	7 (47%)	
M2 (n, %) *	21 (29.6%)	14 (24%)	3 (20%)	
M3 (n, %)*	5 (7%)	2 (4%)	1 (6.7%)	
Core volume(ml)(Median, IQR)	26 (11.5-49.5)	23 (14-48)	15 (11-38)	0.7
Penumbra volume(ml)(Median, IQR)	41 (22.5-58)	46 (32-69)	40 (26-76)	0.3
Relative core volume) (%) †	41 (21-58)	36 (22-50)	25 (17-61)	0.4

Relative penumbra volume (%) †	59 (41-79)	64 (50-78)	75 (39-82)	0.4
penumbra/core ratio (Median, IQR)	1.45(0.6-3.6)	1.8(1-3.6)	3(0.6-4.7)	0.3
Target mismatch (n, %)	39/70 (56%)	43/58 (74%)	10/15 (67%)	0.09
Good collaterals (n, %)	22/56 (39%)	17/47 (36%)	7/15 (47%)	0.9§
Moderate collaterals (n, %)	19/56 (34%)	16/47 (34%)	4/15 (27%)	
Poor collaterals (n, %)	15/56 (27%)	14/47 (30%)	4/15 (27%)	
<p>NIHSS: National Institute of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT score; TIA: Transient Ischemic Attack; ICA: Internal Carotid artery; * Middle Cerebral Artery M1, M2, M3 segments; † proportion (%) of core, penumbra volume(s) in total perfusion lesion volume (core or penumbra volume/ total perfusion lesion volume) × 100). § p value is for a chi-squared analysis of the distribution across all 3 categories.</p>				

Table 2. Univariate linear regression for predictors of relative penumbra volume *

variable	B coefficient (95% CI)	P value
ICA or M1 occlusion	-7(-14-0.4)	0.06
Time to CTP	0.2(-0.3-0.07)	0.5
(Good or moderate) versus poor collaterals	22(14-29)	<0.01
Time* ((good or moderate) v poor collaterals)	0.089 (-0.012-(0.2))	0.08
Diabetes	-11.37(-22-(-0.3))	0.043
NIHSS	-1.5(-1.9-(-1.05))	<0.01
Age	0.034((-0.28)-0.34)	0.8
Blood glucose	-0.75((-0.18)-0.37)	0.18
Systolic blood pressure	-0.089((-0.25)-0.07)	0.2

*Proportion of penumbra volume(s) in total perfusion lesion volume (penumbra volume/ total perfusion lesion volume) × 100).

Table 3. Multivariate linear regression for predictors of relative penumbra volume *

Variable	B Coefficient (95% CI)	P value
NIHSS	-1.19(-1.6-(-0.5))	<0.01
Good or moderate versus poor collaterals	16(8.7-24)	<0.001

* Proportion of penumbra volume(s) in total perfusion lesion volume (penumbra volume/ total perfusion lesion volume) × 100).

