Effect of the Interaction between Recanalization and Collateral Circulation on Functional Outcome in Acute Ischaemic Stroke

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Summary

Identification of patients with acute ischaemic stroke who could most benefit from arterial recanalization after endovascular treatment remains an unsettled issue. Although several classifications of collateral circulation have been proposed, the clinical role of collaterals is still debated. We evaluated the effect of the collateral circulation in relation to recanalization as a predictor of clinical outcome.

Data were prospectively collected from 103 patients consecutively treated for proximal middle cerebral or internal carotid artery occlusion. The collateral circulation was evaluated with a novel semiquantitative-qualitative score, the Careggi collateral score (CCS), in six grades. Both CCS and recanalization grades (TICI) were analysed in relation to clinical outcome. A statistical analysis was performed to evaluate the effect of interaction between recanalization and collateral circulation on clinical outcome.

Out of the 103 patients, 37 (36.3%) had poor collaterals, and 65 (63.7%) had good collaterals. Patients with good collaterals had lower basal National Institute of Health Stroke Scale (NIHSS), more distal occlusion, smaller lesions at 24h CT scan and better functional outcome. After multivariate analysis, the interaction between recanalization and collateral grades was significantly stronger as a predictor of good outcome (OR 6.87, 95% CI 2.11-22.31) or death (OR 4.66, 95%CI 1.48-14.73) compared to the effect of the single variables.

Collaterals showed an effect of interaction with the recanalization grade in determining a favourable clinical outcome. Assessment of the collateral circulation might help predict clinical results after recanalization in patients undergoing endovascular treatment for acute ischaemic stroke.

Introduction

A good outcome in acute ischaemic stroke is known to be associated with prompt reperfusion of the ischaemic area. Reperfusion strategies are focused on the recanalization of vessels through pharmacological lysis or mechanical retrieval of the clot. Recently, three randomised controlled trials on acute phase treatment of ischaemic stroke suggested that an approach mainly based on intra-arterial t-PA and first generation devices for thrombectomy is not superior to intravenous fibrinolysis in improving functional outcome [1-3]. An appropriate selection of patients to be referred for endovascular

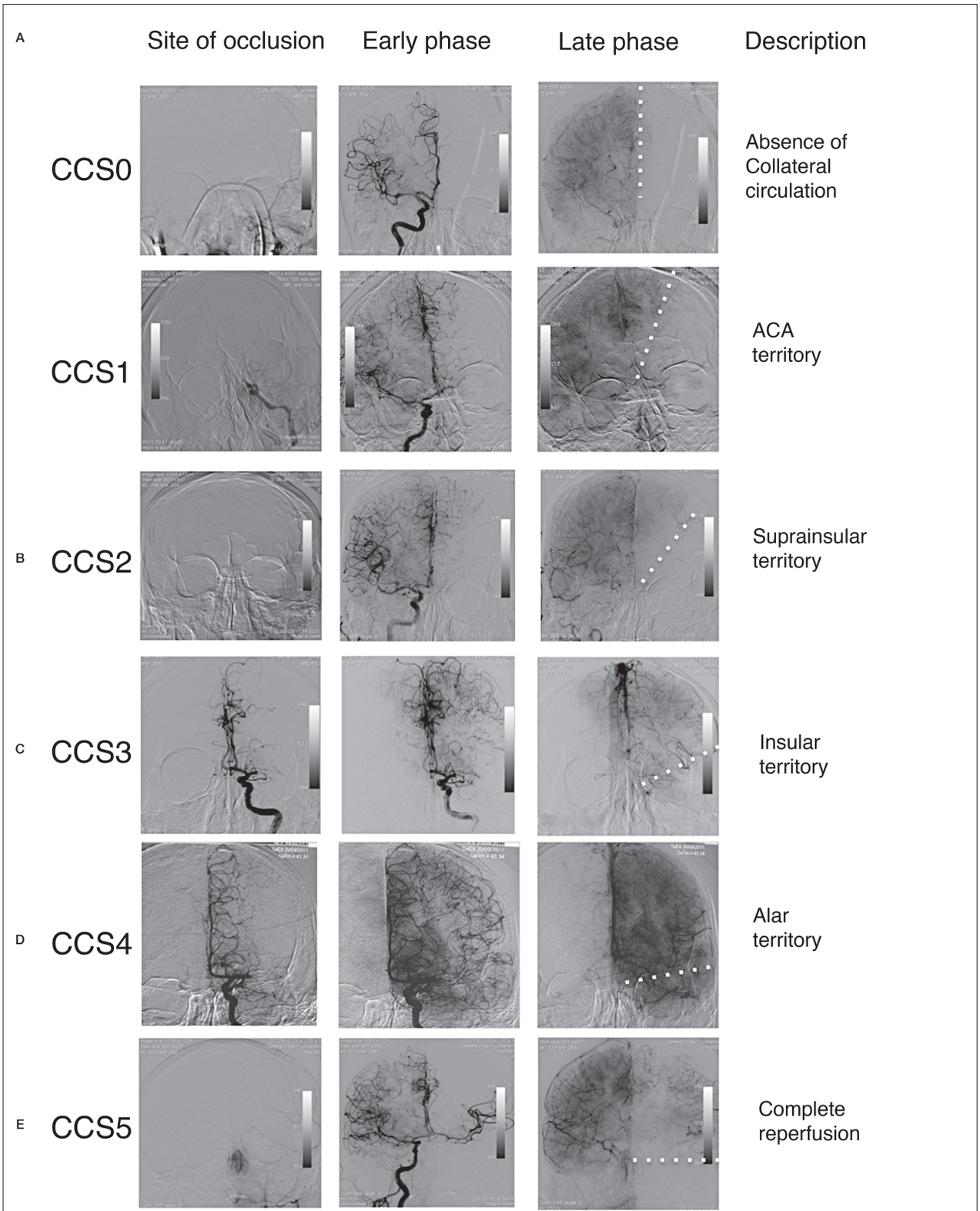

Figure 1 The Careggi collateral score (CCS): semiquantitative evaluation of collateral circulation in anteroposterior projection. Absence of collaterals in left ICA occlusion (CCS=0, image A); collaterals observed until ACA territory in left ICA occlusion (CCS=1, image 1), suprainsular (CCS=2, image B), insular (CCS=3, image C) and alar (CCS=4, image D) territories of the MCA; full cross-flow through the ACoA in left ICA occlusion (CCS=5, image E). A,E) The site of occlusion is the left ICA. B,C) The right MCA is occluded. D) The thrombus is located in the left MCA.

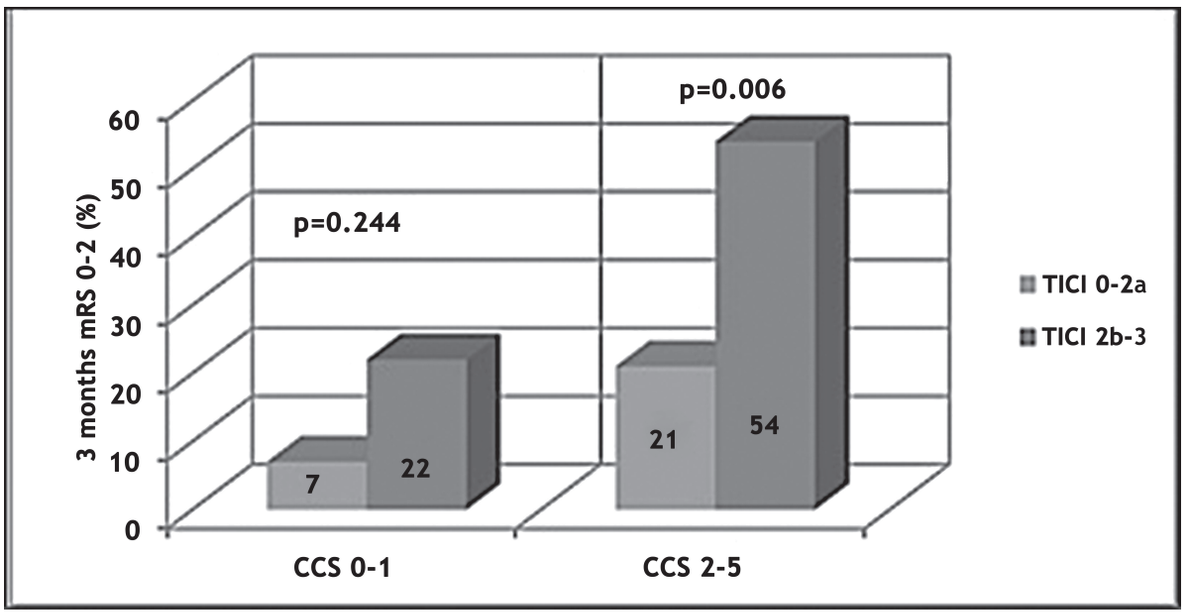

Figure 2 Effect of interaction between reperfusion and collateral circulation on functional outcome. The percentage of patients with a favoUrable clinical outcome is higher in those in whom an adequate recanalization was achieved. Among those in whom a TICI 0-2a grade of recanalization was obtained, the ones with a good CCS (CCS2-5) had higher rates of functional independence after 3 months.

treatment (ET) is a key element to achieve a favourable outcome. In the acute pre-treatment phase of ischaemic stroke, collateral circulation allows the complete or partial perfusion of the ischaemic area beyond the clot, and contributes to the survival of the ischaemic penumbra [4]. Some authors found that pial collateral circulation at digital subtraction angiography was correlated with the reduction of the infarcted area in 36 patients with middle cerebral artery (MCA) occlusion [5] and that good collateral circulation resulted in less severe neurological deficits at baseline [6]. Differences between imaging-based endpoints and functional outcome of patients need to be pointed out, since a clinical recovery does not always follow recanalization or infarct size reduction. A few studies have focused attention on the clinical outcome of patients. Kucinski et al. [7] stated that good collateral circulation independently predicted good outcome in a series of patients treated with IV and IA thrombolysis. Some authors investigated pial collateral circulation through a new grading scale, finding an association between good pial collateral circulation and both good functional outcome and the reduction of haemorrhage at 24h CT scan [8-10]. The aim of this paper was to evaluate the role of recanalization, pial collateral circulation and their interaction on the functional outcome of patients treated with an endovascular approach for acute ischaemic stroke.

Methods

We analysed consecutive patients admitted to a tertiary stroke centre from 1st February 2004 to 31st August 2012 for acute ischaemic stroke who underwent ET. Patients with major anterior circulation vessels occlusion, namely internal carotid artery (ICA) and MCA occlusion, were recruited. Isolated occlusions of M2 branches and distal embolisms (M3) were excluded. All patients were excluded from IV thrombolysis according to the internal protocol of our hospital for the selection of patients in the acute phase of ischaemic stroke. In brief, all patients between three and six hours from symptoms onset, or within three hours but with major exclusion criteria according to the SITS-MOST protocol were considered eligible for endovascular treatment, also considering that regulatory approval was not granted in Italy until October 2013. Clinical data were prospectively collected on a web-based registry, including demographic data, symptoms onset, time of arrival at the Emergency Department, acute phase parameters, blood examination, National Institute of Health Stroke Scale (NIHSS) as-

sessment, time to CT scan, time to endovascular treatment. NIHSS was collected daily during the hospital stay and at discharge; clinical follow up was performed after three months with modified Rankin Scale (mRS). Neuroimaging data were retrospectively analysed. Basal CT scans and 24-48 hour CT scans were reviewed by a vascular neurologist (VP) to evaluate ASPECTS and spontaneous vessels hyperdensity. We used ASPECTS both on pre-treatment and 24-48 hour CT scan to assess early ischaemic changes and extension of infarction. Additional CT scans were performed when neurological deterioration was observed. An interventional neuroradiologist (SM), blinded to clinical data, reviewed angiograms. On pre-treatment angiograms the site of occlusion and the presence and extension of collateral circulation were evaluated. For this purpose we created a semiquantitative score, named Collateral circulation score (CCS) [11]. In case of complete supraclinoid ICA occlusion, collateral circulation was assessed injecting the contralateral ICA to visualize any cross-flow through the anterior communicating artery (ACoA) and the anterograde filling of the contralateral hemisphere. Since only a few patients underwent a complete pre-treatment angiographic assessment, including vertebral artery injection, pial collateral circulation from the posterior cerebral artery was not considered. However, when the posterior circulation was studied the role of posterior collateralization resulted marginal or minimally effective to fill the whole MCA territory retrogradely. Based on the extension of anterograde filling of the anterior cerebral artery (ACA) and retrograde filling of MCA territory in antero-posterior projection, this score identifies six degrees of collateralization: 0=no flow in both ACA and MCA territory; 1=flow in ACA territory; 2=flow in MCA territory, above the insular region; 3=flow in MCA territory, including the insular region; 4=flow in M1 segment of MCA; 5= cross-flow in MCA territory through the ACoA [Figure 1]. Although grade 5 may not be considered a leptomeningeal collateralization, it represents the highest grade of compensation to a major intracranial occlusion and was included in the analysis. All the angiographic series were performed, also including the late venous phases, to visualize the maximum grade of collateralization. A qualitative analysis was performed on lateral projection to detect fragmented and suspended collateral arteries that were interpreted as "regressive" signs of slow and hindered blood flow. In the presence of regressive signs, the assigned score was reduced by 1 point. Therefore, the final (named "pure") score is the sum of quantitative and qualitative analysis (i.e. CCS 3 with regressive signs means pure CCS 2). We dichotomized collateral circulation into poor, from degree 0 to degree 1 of pure CCS, and good for degrees from 2 to 5. An interventionalist with 30 years' experience reviewed all pre-and post-treatment angiograms to assess the CCS and the recanalization rate, blinded to clinical data, using the Thrombolysis In Cerebral Infarction (TICI) score. TICI was dichotomised in 0-2a and 2b-3 to indicate absent/partial and adequate recanalization respectively. Good outcome was defined as mRS ≤ 2 at 90 days. Early clinical improvement, defined as a decrease of ≥ four points at 24h NIHSS or 24h NIHSS= 0, was also considered a measure of early outcome. Intracranial haemorrhage was considered symptomatic (sICH) in the presence of ≥ four points increase at NIHSS associated with any haemorrhage at 24h CT scan. The extension of parenchymal haemorrhage at 24h CT scan according to SITS-MOST criteria was also assessed. Clinical and neuroradiological data were compared between the two groups according to collateral distribution. Continuous variables were reported as mean ± standard deviation and median (interquartile range); categorical variables were reported as proportions. A ROC curve was performed to identify a cut-off value, that resulted CCS=1. Differences in continuous variables were analysed with the analysis of variance, while χ^2 test was used to assess differences in categorical variables. Univariate analysis was performed to evaluate clinical-instrumental variables possibly associated with the presence of collateral circulation and clinical outcome. A stepwise logistic regression model was used to identify independent predictors of favourable outcome and death. Statistical analysis was performed using SPSS software (IBM) version 20.0.

Results

The study population included 103 patients, 64 (62.1%) with proximal (before the origin of lenticulostriate arteries) and/or distal M1-MCA occlusion ± M2, and 39 (37.9%) with T-siphon occlusion, defined as intracranial ICA associated with M1-MCA and A1-ACA occlusion.

Baseline characteristics of the study population were median age 61 (iqr 60-77) years and male sex in 55 (53.4%) patients. Median baseline NIHSS was 20 (iqr 17-24). Fifty-six (54%) patients received thrombectomy, 42 (41%) multimodal endovascular treatment, including mechanical disruption/retrieval of the clot and intra-arterial fibrinolytics, while only five (5%) patients were treated with intra-arterial fibrinolytics. Nineteen (18%) patients received ET as a rescue therapy after IV thrombolysis. According to collaterals distribution, 37 (35.9%) patients presented poor collaterals and were graded as pure CCS 0-1, while 66 (64.1%) patients with good collaterals were graded as pure CCS 2-5. There were no significant differences for age, gender, systolic and diastolic arterial blood pressure, time from symptoms onset to groin puncture or basal ASPECTS between patients with poor and good collaterals (Table 1). Median baseline NIHSS was higher in the poor with respect to the good collaterals group (23, iqr 20-27 vs 18, iqr 16-22; p<0.001). As for the site of occlusion, T-siphon occlusion was more represented in patients with poor collaterals (70.3% vs 19.7% in the good collaterals group), while proximal and distal MCA occlusions occurred more frequently in the good collaterals group (80.3% vs 29.7% in the poor collaterals group), p<0.001. There was no difference in the distribution of vascular risk factors between the two groups (Table 2). Outcome measures according to collateral distribution are shown in Table 3. Favourable outcome at three months was more frequently achieved by the good collaterals group patients (33.8% vs 10.8% in the poor collaterals group, p=0.010). Ischaemic lesion extension at 24h CT scan was smaller in the good collaterals group patients (mean ASPECT 4.9±2.6 vs 3.2±2.9 in the poor collateral group, p=0.009). No statistically significant differences in early clinical improvement, reperfusion rates and procedural adverse events were observed between patients with good and poor collaterals (Table 3). The death rate differed between the two groups (35.1% vs 18.5% respectively in patients with poor and good collaterals, p=0.06). At univariate analysis, variables associated with favourable outcome were younger age, lower baseline NIHSS, higher collateral grading, more proximal site of occlusion,

Table 1 **Baseline clinical and instrumental features according to collateral circulation in 103 patients in Careggi Hospital registry. Collateral score dichotomised into poor (CCS 0-1) and good (CCS 2-5).**

	Total N=103	**CCS 0-1** N=37	**CCS 2-5** N=66	**P**
Age	71 (60-77)	70 (60-76)	72 (60-78)	0.677
Gender M	55 (53.4%)	16 (43.2%)	39 (59.1%)	0.122
Baseline NIHSS	20 (17-24)	23 (20-27)	18 (16-22)	< 0.001
Systolic blood pressure	161.1 ± 25.1	154.9 ± 25.8	163.4 ± 24.7	0.225
Diastolic blood pressure	81.2 ± 14.5	77.1 ± 13.9	82.7 ± 14.6	0.163
Time to groin puncture *	270 (223-311)	270 (201-320)	270 (233-310)	0.920
Time to groin puncture **				
0-4.5h	55 (53.9%)	20 (54.1%)	35 (53.8%)	0.905
4.5-6h	35 (34.3%)	13 (35.1%)	22 (33.8%)	
> 6h	12 (11.8%)	4 (10.8%)	8 (12.3%)	
Baseline ASPECTS °	7.7 ± 1.9	7.3 ± 2.2	7.9 ± 1.7	0.150
Site of occlusion				
T-siphon §	39 (37.9%)	26 (70.3%)	13 (19.7%)	< 0.001
M1 MCA^	42 (40.8%)	10 (27.0%)	32 (48.5%)	
M1-M2 MCA #	22 (21.3%)	1 (2.7%)	21 (31.8%)	

*Data expressed as n (%), mean ± SD or median (iqr). * median time from symptoms onset to treatment (minutes)*
*** categorized time from symptoms onset to treatment (hours); ° median values of early ischaemic changes at baseline; § occlusion of intracranial internal carotid artery and M1 middle cerebral and A1 anterior cerebral arteries; ^ occlusion of M1 middle cerebral artery proximal to the lenticulostriate arteries ± internal carotid artery; # occlusion of M1 middle cerebral artery distal to lenticulostriates ± M2 segment.*

Table 2 **Vascular risk factors according to collateral circulation in 103 patients in Careggi Hospital registry. Collateral score dichotomised into poor (CCS 0-1) and good (CCS 2-5).**

	Total N=103	**CCS 0-1** N=37	**CCS 2-5** N=66	**P**
Hypertension	59 (57.8%)	20 (54.1%)	39 (60.0%)	0.559
Diabetes	17 (17.2%)	5 (13.5%)	12 (18.5%)	0.519
Dyslipidaemia	25 (24.5%)	9 (24.3%)	16 (24.6%)	0.974
Smoking	28 (27.5%)	8 (21.6%)	20 (30.8%)	0.320
Coronary artery disease	14 (13.7%)	6 (16.2%)	8 (12.3%)	0.581
Atrial fibrillation	36 (35.3%)	14 (37.8%)	22 (33.8%)	0.685
Valvulopathy	9 (8.8%)	5 (13.5%)	4 (6.2%)	0.208
Congestive heart failure	4 (3.9%)	1 (2.7%)	3 (4.6%)	0.632

Table 3 **Measures of clinical and instrumental outcomes according to collateral circulation in 103 patients in Careggi Hospital registry. Collateral score dichotomised into poor (CCS 0-1) and good (CCS 2-5).**

	Total N=103	**CCS 0-1** N=37	**CCS 2-5** N=66	**P**
Early improvement (NIHSS) *	40/101 (39.6%)	11/36 (30.6%)	29/65 (44.6%)	0.166
mRS 0-2 (independence)	26/102 (25.5%)	4/37 (10.8%)	22/65 (33.8%)	0.010
mRS 6 (death)	25/102 (24.5%)	13/37 (35.1%)	12/65 (18.5%)	0.060
Complete reperfusion (TICI 2b-3)	35/103 (34.0%)	9/37 (24.3%)	26/66 (39.4%)	0.121
Lesion extension (ASPECTS)	4.4 ± 2.8	3.2 ± 2.9	4.9 ± 2.6	0.009
Symptomatic haemorrhage (ECASS) §	13/103 (12.6%)	6/37 (16.2%)	7/66 (10.6%)	0.411
Instrumental haemorrhage (PH1-PH2)	15/103 (14.6%)	6/37 (16.2%)	9/66 (13.6%)	0.722
Symptomatic haemorrhage (SITS-MOST)	5/103 (4.9%)	3/37 (8.1%)	2/66 (3.0%)	0.250
Procedural adverse events ^	9/103 (8.7%)	4/37 (10.8%)	5/66 (7.6%)	0.577

*Data expressed as n (%) or mean ± SD. mRS: 3 months modified Rankin Scale; * Decrease of at least 4 points at 24h NIHSS or 24h NIHSS equal to 0; # mean values of 24h ASPECTS; § any intracranial haemorrhage associated with ≥ 4 point increase at NIHSS; ^ includes vessel dissectionand subarachnoid haemorrhage.*

higher rates of early clinical improvement, higher degrees of reperfusion, reduced extent of infarction at 24h CT scan, and symptomatic intracranial haemorrhage. Variables associated with death were older age, lower baseline ASPECTS, T-siphon as occlusion site, lower rates of early clinical improvement, higher rates of symptomatic intracranial haemorrhage (Tables 4 and 5). A stepwise logistic regression analysis showed that the interaction between reperfusion and collateral circulation was stronger as a predictor of good outcome (OR 6.87, 95% CI 2.11-22.31) or death (OR 4.66, 95% CI 1.48-14.73), compared to collateral circulation or reperfusion considered as single variables (Table 6). Finally, independently from the grade of recanalization obtained, a linear correlation between favourable clinical outcome and the CCS grade was observed (OR 1.76, (CI 95%, 1.10-2.82) with the probability of good outcome increased by an OR of 1.76 (CI 95% 1.10-2.82) for each CCS grade.

Discussion

The role of the collateral circulation was analysed with regard to pre-, post- and treatment-related variables. The severity of clinical status at admission seemed to be associated with the extent of pial collateral circulation: the comparison between the two groups of patients dichotomized for CCS grade (0-1 vs 2-5) showed a significant difference of more than four points at NIHSS, with higher scores within the CCS 0-1 group. This is in line with current literature, and highlights the role of the collateral circulation in preserving viable tissue [12]. The CCS is

Table 4 **Baseline clinical and instrumental features according to clinical outcome at 3 months and death in 103 patients in Careggi Hospital registry with completed follow-up. Outcome dichotomised: favourable (mRS 0-2), unfavourable (mRS 3-6).**

	Total N=103	mRS 0-2 N=26	mRS 3-6 N=77	P	Death N=25	Alive N=78	P
Age	71 (60-77)	54 (43-69)	74 (62-80)	< 0.001	74 (61-81)	67 (54-76)	< 0.001
Gender M	54 (52.9%)	17 (65.4%)	37 (48.7%)	0.141	11 (44.0%)	43 (55.8%)	0.303
Baseline NIHSS	21 (17-24)	18 (16-22)	22 (18-25)	0.005	22 (15-27)	20 (17-23)	0.370
Systolic blood pressure	160.8 ± 25.1	163.0 ± 23.0	159.9 ± 26.1	0.657	160.5 ± 27.3	160.9 ± 24.6	0.957
Diastolic blood pressure	81.0 ± 14.6	79.6 ± 12.5	81.6 ± 15.4	0.625	85.6 ± 14.1	79.5 ± 15.6	0.137
Time to groin puncture*	270 (225-312)	270 (236-312)	270 (210-315)	0.810	258 (199-296)	270 (225-317)	0.395
Time to groin puncture ** 0-4.5h	54 (53.5%)	14 (53.8%)	40 (53.3%)	0.791	14 (58.3%)	40 (51.9%)	0.498
4.5-6h	35 (34.7%)	8 (30.8%)	27 (36.0%)		8 (33.3%)	27 (35.1%)	
>6h	12 (11.9%)	4 (15.4%)	8 (10.7%)		2 (8.3%)	10 (13.0%)	
Baseline ASPECTS°	7.7 ± 1.9	8.0 ± 1.7	7.6 ± 1.9	0.379	7.0 ± 2.4	8.0 ± 1.7	0.026
Good collateral score#	65 (63.7%)	22 (84.6%)	43 (56.6%)	0.010	12 (48.0%)	53 (68.8%)	0.06
Site of occlusion T-siphon§	39 (38.2%)	3 (11.5%)	36 (47.4%)	0.005	15 (60.0%)	24 (31.2%)	0.038
M1 MCA^	41 (40.2%)	15 (57.7%)	26 (34.2%)		6 (24.0%)	35 (45.5%)	
M1-M2 MCA#	22 (21.6%)	8 (30.8%)	14 (18.4%)		4 (16.0%)	18 (23.4%)	

*Data expressed as n (%), mean ± SD or median (iqr). * median time from symptoms onset to treatment (minutes); ** categorized time from symptoms onset to treatment (hours); ° mean values of early ischaemic changes at baseline; #collateral circulation score 2-5; § occlusion of intracranial internal carotid artery and M1 middle cerebral and A1 anterior cerebral arteries; ^ occlusion of M1 middle cerebral artery proximal to the lenticulostriate arteries ± internal carotid artery; # occlusion of M1 middle cerebral artery distal to lenticulostriates ± M2 segment.*

strongly influenced by the site of occlusion; in particular, occlusion of the ACA (A1 segment) together with the MCA in carotid T-occlusion would limit the possibility of a pial retrograde collateral circulation provided by the ACoA. We did not find any association between the extent of collateral circulation and other baseline features of the population in study. In particular, the distribution of CCS was not influenced by age, hypertension or other vascular risk factors [13], differently from previous reports [14-17]. Nor was the distribution of the collateral circulation influenced by the time of ischaemia, and that could be explained if we consider that the presence of collaterals mainly depends on individual pre-existing anatomy. Although an association between pre-treatment collateral circulation and clinical severity at admission was observed, our results did not show a relationship between pial collaterals and baseline CT findings. A possible interpretation of this datum could be given considering the poor sensitivity of CT to detect early ischaemic signs in hyperacute ischaemia. Furthermore, the CCS is based on leptomeningeal anastomoses and therefore it does not consider the involvement of deep territories, such as the basal ganglia, that represent 3/10 points of the ASPECT score. As previously reported, the degree of collateral circulation resulted as a predictor of the extension of the ischaemic area, evaluated with ASPECTS on 24 hour CT scan, that was lower in patients with an insufficient collateral score. In our series there was no significant association between the poor grade of the collateral circulation, symptomatic intracranial haemorrhage and parenchymal haematoma, differently from data reported in literature [9,18], even if this could be due to the numerosity of the study population. Concerning the treatment-related variables we found that besides age, complete reperfusion and the presence of pial collateral circulation were the only independent predictors of good functional outcome,

Table 5 **Measures of clinical and instrumental outcomes according to clinical outcome at 3 months and death in 103 patients in Careggi Hospital registry with completed follow-up. Outcome dichotomised: favourable (mRS 0-2), unfavourable (mRS 3-6).**

	Total N=103	mRS 0-2 N=26	mRS 3-6 N=77	P	Death N=25	Alive N=78	P
Early improvement *	40/100 (40.0%)	23/26 (88.5%)	17/74 (23.0%)	< 0.001	2/20 (10.0%)	38/75 (50.7%)	0.001
Complete reperfusion °	35/103 (34.3%)	16/26 (61.5%)	19/76 (25.0%)	0.001	7/25 (28.0%)	28/78 (36.4%)	0.444
Lesion extension #	4.3 ± 2.8	6.1 ± 2.8	3.5 ± 2.7	< 0.001	3.2 ± 3.0	4.6 ± 2.6	0.075
Symptomatic haemorrhage (ECASS) §	13/103 (12.7%)	0/26 (0.0%)	13/77 (17.1%)	0.024	7/25 (28.0%)	6/78 (7.8%)	0.008
Instrumental haemorrhage (PH1-PH2)	15/103 (14.7%)	2/26 (7.7%)	13/76 (17.1%)	0.242	6/25 (24.0%)	9/78 (11.7%)	0.131
Symptomatic haemorrhage (SITS-MOST)	5/103 (4.9%)	0/26 (0.0%)	5/77 (6.6%)	0.180	3/25 (12.0%)	2/78 (2.6%)	0.059
Procedural adverse events ^	9/103 (8.8%)	1/26 (3.8%)	8/77 (10.5%)	0.300	4/25 (16.0%)	5/78 (6.5%)	0.145

*Data expressed as n (%) or mean ± SD. * Decrease of at least 4 points at 24h NIHSS or 24h NIHSS equal to 0; ° TICI 2b-3; # mean values of 24h ASPECTS; § any intracranial haemorrhage associated with ≥4 point increase at NIHSS; ^ includes vessel dissection and subarachnoid haemorrhage.*

Table 6 **Multivariate analysis for the prediction of favourable outcome (modified Rankin Scale 0-2 at 3 months) or death (modified Rankin Scale 6 at 3 months) in 103 patients in Careggi Hospital registry with completed follow-up.**

Favourable outcome	Without interaction		With interaction	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	0.92 (0.88 – 0.96)	< 0.001	0.92 (0.88 – 0.96)	< 0.001
Reperfusion (TICI 2b-3 vs. TICI 0-2a)	4.19 (1.35 – 12.97)	0.013	Not selected	
Collaterals (CCS 2-5 vs. CCS 0-1)	4.55 (1.21 – 17.17)	0.025	Not selected	
Reperfusion by collaterals	-	-	6.87 (2.11 – 22.31)	0.001

Death	Without interaction		With interaction	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.11 (1.05 – 1.18)	0.001	1.12 (1.05 – 1.19)	0.001
Reperfusion (TICI 0-2a vs. TICI 2b-3)	Not selected		Not selected	
Collaterals (CCS 0-1vs. CCS 2-5)	3.80 (1.28 – 11.26)	0.016	Not selected	
Reperfusion by collaterals	-	-	4.66 (1.48 – 14.73)	0.009

Logistic regression analysis (stepwise method). Variables in the analysis: age, baseline NIHSS, time to groin puncture, site of occlusion, reperfusion grades and collateral grades. Table only shows variables included in the model.

with a joint effect. The survival of an ischaemic area may depend on the site of occlusion and the presence of a collateral circulation, and these two factors, together with the grade of reperfusion at the end of ET, may determine the patient's clinical outcome. The rate of rep-

erfusion after acute phase treatments of stroke is generally accepted as a surrogate marker of good clinical outcome [19]. We observed that collateral circulation is also able to influence clinical outcome with a chance to achieve a good functional outcome after three months increased by 76% for each CCS crescent point. Our data showed no significant differences in terms of adequate reperfusion (TICI 2b-3) between the two groups and the hypothesis that a patient with a good collateral score may have higher possibilities of reperfusion could not be supported. Therefore, both the grade of reperfusion and the grade of collaterals should be considered independent predictors of good clinical outcome. Indeed, considering a dichotomization of our study population into "recanalized" and "not recanalized" patients, favourable clinical outcomes may also be observed in patients without effective recanalization when a sufficient collateral circulation is present (in 21/103 patients; 20%). Conversely, when an adequate recanalization is achieved the presence or absence of a collateral circulation may determine different rates of favourable clinical outcome (poor vs good collaterals in recanalized patients: 22/103, 21.3% vs 54/103, 52.4%) (Figure 2). In our study, the collateral circulation and effective recanalization seem to have a joint effect on clinical outcome: the interaction of these two factors provided better functional outcomes in patients undergoing ET. In the same way, although mortality was not significantly different between the two groups (p=0.06) the presence of poor collaterals in poor or absent recanalization seems to be strongly associated with higher death rates. Stepwise logistic regression analysis (Table 6) showed that the interaction between recanalization and CC grades was significantly stronger as a predictor of good functional outcome or death, compared to CC or recanalization grade alone. This interaction may be related to the concept of "futile recanalization", described as the restoration of flow in a hypoperfused area not adequately supplied by a good collateral circulation, with unfavourable clinical outcome. Bang et al. also investigated the relationship between collaterals and recanalization, reporting a correlation between a good collateral circulation and the improvement in recanalization rate after ET [20], but did not evaluate clinical outcome. Based on these assumptions it would also be important for the prognostic prediction of ET not only to establish the presence of the pial collateral circulation but also to quantify the effectiveness of the collateral circulation with an adequate score, which could be in some way correlated with the extension of the ischaemic penumbra. Recently, Demchuk et al. proposed the "3C approach", including the evaluation of the core, clot, and collateral (3C) based on a NCCT/CT angiography protocol. This quick evaluation would help to identify the best profile of patient (small core, large clot and good collaterals) to be referred to ET, thus improving the selection of patients for acute stroke treatment [21]. Further studies will be needed to establish this kind of correlation by means of an adequate neuroimaging protocol. Unfortunately, given the lack of a uniform grading system for collateral circulation, the relevance of its role in determining the outcome of patients has not been unequivocally established. A review by Liebeskind et al. found an extreme variability in the scales used to assess collateral circulation, with 81 publications describing 63 different methods for grading collateral flow. According to the authors, inconsistency in evaluating collateral flow could lead to an underestimation of the role of the collateral circulation in outlining the outcome of acute stroke patients [22]. We believe that further efforts are required in this direction and, possibly, to identify clinical baseline features predicting good collateral circulation in acute stroke patients.

The limitations of the present study include its single centre nature, which could prevent the results being generalized. Moreover, retrospective analysis of neuroimaging could have limited the availability of good quality material, reducing the sample. In addition, the different endovascular techniques used during the long term of inclusion of the cases evaluated may have determined different possibilities to achieve adequate recanalization rates. Expert evaluation of neuroimaging is the major strength of this study, together with the prospective collection of clinical data and follow-up. This allows the protocol to be replicated in different settings to confirm our findings. Data from the present study suggest that evaluation of the collateral circulation should be routinely performed in candidates for ET. This approach could help identify an ideal profile of patient to be referred to ET, reducing the use of aggressive revascularization strategies in patients with poor collateral circulation, who could even be harmed by late, futile recanalization. At the

same time, the attempt to reach high recanalization rates could be justified in patients with good collateral circulation, who are more likely to benefit from the reperfusion process.

Conclusions

There is accumulating evidence that the collateral circulation has a protective effect on the evolution of the ischaemic area and seems to influence clinical outcome independently from the grade of recanalization.

The recanalization grade remains an independent predictor of favourable outcome, although its clinical effectiveness seems to be related to the presence of a good collateral circulation. Based on our findings, the interaction between good collateral score and adequate recanalization may be considered an independent predictor of favourable clinical outcome.

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