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Effect of collateral blood flow on patients undergoing endovascular therapy for acute ischemic stroke

Michael P. Marks, MD, **Maarten G. Lansberg, MD**, **Michael Mlynash, MD**, **Jean-Marc Olivot, MD**, **Matus Straka, PhD**, **Stephanie Kemp, BS**, **Ryan McTaggart, MD**, **Manabu Inoue, MD**, **Greg Zaharchuk, MD, PhD**, **Roland Bammer, PhD**, **Gregory W. Albers, MD**, and **for the DEFUSE 2 Investigators**

Stanford Stroke Center, Stanford University School of Medicine, Palo Alto, CA

Abstract

Background and Purpose—Our aim was to determine the relationships between angiographic collaterals and diffusion/perfusion findings, subsequent infarct growth, and clinical outcome in patients undergoing endovascular therapy for ischemic stroke.

Methods—Sixty patients with a TICI score of 0, 1 and ICA/M1 occlusion at baseline were evaluated. A blinded reader assigned a collateral score using a prior 5 point scale, from 0 (no collateral flow) to 4 (complete/rapid collaterals to entire ischemic territory). Analysis was dichotomized to poor flow (0–2) versus good flow (3–4). Collateral score was correlated with baseline NIHSS, DWI volume, PWI volume (Tmax ≥ 6 sec), TICI reperfusion, infarct growth and mRS at day 90.

Results—Collateral score correlated with baseline NIHSS (p=0.002) and Tmax ≥ 6 sec volume (p=0.009). 29% of patients with poor collateral flow had TICI 2B-3 reperfusion versus 65.5% with good flow, p=0.009. Patients with poor collaterals who reperfused (TICI 2B-3) were more likely to have a good functional outcome (mRS 0–2 at 90 days) than patients who did not reperfuse, OR 12 (95% CI, 1.6–98). There was no difference in the rate of good functional outcome following reperfusion in the patients with poor collaterals versus good collaterals (p= 1.0). Patients with poor reperfusion (TICI 0–2a) showed a trend toward greater infarct growth if they had poor collaterals vs. good collaterals, p=0.06.

Conclusion—Collaterals correlate with baseline NIHSS, PWI volume, and good reperfusion. However, Target Mismatch patients who reperfuse, appear to have favorable outcomes at a similar rate, irrespective of the collateral score.

Keywords

collateral circulation; acute stroke; angiography; acute Rx; magnetic resonance imaging

Corresponding Author: Michael P. Marks, MD, Professor of Radiology and Neurosurgery, Stanford University Medical Center, 300 Pasteur Drive, Room S-047, Stanford, California 94305-5105, mmarks@stanford.edu, t:650-723-6767.

Introduction

Endovascular therapy has emerged as a principal approach to blood flow restoration in acute ischemic stroke. MRI evaluation of patients for DWI-PWI mismatch has been suggested as a non-invasive imaging study to help select patients for reperfusion therapy, particularly in a later time window.[1–3] Good angiographic collaterals have been associated with improved recanalization and a lower incidence of hemorrhagic transformation following endovascular therapy.[4–6] We undertook this study to determine the relationship between angiographic collaterals and MR based diffusion-perfusion imaging, angiographic reperfusion, subsequent infarct growth, and clinical outcome in patients undergoing endovascular therapy for acute ischemic stroke.

Methods

Patients with acute anterior circulation strokes which could be treated using endovascular therapy within 12 hours of ictus were enrolled in the DEFUSE 2 study from July 2008 to September 2011. They underwent baseline MRI imaging on 1.5 or 3.0 T MR systems and were eligible for enrollment if they had a large vessel occlusion. Image reconstruction was done with an off-line computer to produce quantitative DWI and PWI lesion maps (RAPID).[7] An early follow up MR was done within 12 hours of completing endovascular therapy. An additional MRI study was obtained at discharge or on day 5 and included a fluid-attenuated inversion recovery (FLAIR) sequence which was used to determine infarct volume.

The automated maps included a defined measure of the ischemic core volume which was the region of the acute DWI lesion with an apparent diffusion coefficient (ADC) of $< 600\times10^{-6}mm^2/sec$. The automated maps also included a measure of hypoperfused tissue which was derived from the PWI maps as the region with a time to maximum of the tissue residue function (Tmax) of ≥ 6 seconds. These values for estimated ischemic core and critically hypoperfused tissue were previously validated.[7–9] The Target mismatch profile (TMM) was pre-defined as a ratio between the hypoperfused tissue and ischemic core of ≥1.8, with an absolute difference of ≥ 15 ml. In addition, patients with a TMM profile also had to have an ischemic core volumes < 70 ml and the volume of tissue with more severe hypoperfusion (Tmax > 10 seconds) had to be < 100 ml.

Endovascular Treatment

Patients started endovascular treatment within 12 hours of ictus and 1.5 hours of the baseline MRI. The use of FDA approved devices for thrombectomy, including the Concentric Merci Retriever and the Penumbra Suction Thrombectomy catheter, was encouraged however no device or procedural method was required. Investigators were encouraged to minimize IA-tPA use. If patients had been treated with intravenous tPA, a maximum dose of ≤ 5 mg of intra-arterial tPA was recommended. If no systemic tPA had been administered, investigators were asked to consider using ≤ 25 mg intra- arterially.

Imaging Evaluation

Infarct growth was determined based on the change between the baseline DWI lesion volume and the volume determined from the FLAIR image at 5 days. Hemorrhagic transformation for parenchymal hematoma formation (PH1 and PH2)[10] was evaluated from any follow-up CT or MRI done within 7 days of stroke onset. A single reader, blinded to angiographic and clinical outcome, evaluated the baseline angiogram prior to treatment. The primary arterial occlusive lesion (AOL) was assigned and a thrombolysis in cerebral infarction (TICI) score was also assigned using previously published definitions.[11,12] Patients with baseline TICI 0, 1 flow and occlusions in the ICA or M1 segment of the MCA were included in this analysis. Collateral scoring of the baseline angiogram was done using a previously defined 5 point system where 0 is no collateral flow and 4 is complete and rapid collateral flow to the ischemic territory.[11] Only those angiograms which were judged to contain adequate information to judge collateral circulation were included. Imaging through the venous phase had to be available. The final post-treatment angiogram was also evaluated for a TICI score. The TICI score assigned used a definition for TICI that 2A was partial reperfusion ≤ 50% of the vascular territory of the occluded artery and 2B which was partial reperfusion of > 50% of the occluded artery.[12]

Statistics

We compared rates of good outcome between groups using Fisher's exact test. We used the Cohran-Armitage test to evaluate trends in the rates of good outcome with increasing reperfusion scores; we used Jonckheere-Terpstra test to evaluate similar trends for continuous variables. Comparisons were made across the entire group of collateral scores and we also dichotomized collateral scores into a good collateral group (scores of 3 and 4) versus a poor collateral group (scores of 0–2). Lesion growth between dichotomized groups was analyzed with the Mann-Whitney U test. We also conducted logistic regression analysis (for TICI 2b-3 reperfusion) and median regression analysis (for baseline NIHSS, Tmax>6s lesion size, and lesion growth) with collaterals status and the site of the occluded artery entered as predicting factors. All tests were two-tailed and considered significant at $\alpha<0.05$ level. Statistical analysis was done using SAS 9.3 (SAS Institute Inc., CARY, NC).

Results

Table 1 shows the demographic values for the study group. There was a significant difference in the incidence of good collaterals based on the location of occlusion ($p<0.001$). There was also significant difference in the baseline NIHSS scores between the patients with poor collaterals and those with good collaterals ($p= 0.025$). Figure 1 shows the mean NIHSS score for each collateral score. There was a significant decline in the NIHSS across the range of collateral scores from lower to higher ($p=0.002$).

The collateral score from the baseline angiogram was correlated with the Tmax perfusion delay volume on the baseline MR scan (obtained prior to endovascular therapy). Specifically, the lesion size defined by time to maximum of the tissue residue function (Tmax) threshold of ≥ 6 seconds was correlated with the collateral scores as shown in Figure 2. Across the full range of collateral scores there was a correlation between higher collateral

scores and lower PWI lesion volumes (p=0.009). The median volume of tissue with Tmax ≥6 sec for good collaterals was 82 (IQR, 51–109) ml versus 115 (74–136) ml for patients with poor collaterals, [p = 0.012]. A similar analysis comparing collateral scores with the baseline DWI lesion volume did not show a correlation between collateral scores and DWI lesion volume across the range of collateral scores or by stratifying collateral scores dichotomously. We also examined the relationship between collateral score and the ratio of the Tmax ≥ 6 sec lesion volume to the DWI lesion volume and did not find that collateral scores correlated with this ratio.

Table 2 shows the TICI reperfusion scores for patients stratified by good or poor collateral scores. There was shift to higher rates of reperfusion with good collaterals (p=0.010). Patients with good collateral scores had significantly higher rates of TICI 2B-3 reperfusion (65.5%) versus those with poor collateral scores (29%), [p=0.009].

The relationship between the volume of infarct growth seen on the 5 day follow-up imaging study and the collateral scores for Target mismatch patients is shown in Figure 3. Patients with poor collaterals (0–2) and good reperfusion (TICI 2B-3) had significantly less infarct growth compared to those with poor reperfusion (TICI 0–2A), [p=0.009]. Patients with good collateral scores (3–4) had less infarct growth with good reperfusion compared to those that had poor reperfusion, but the difference was not significantly different (p=0.25). There was also a strong trend for the amount of infarct growth being greater in the patients with poor collateral who did not reperfuse well versus those with good collaterals who did not reperfuse well (p=0.06). However there was no difference in the amount of infarct growth comparing those with poor and good collaterals who reperfused (p=0.73).

Table 3 shows the 90 day good functional outcome rates in Target mismatch patients with good and poor collaterals stratified by whether they had good or poor reperfusion. Significantly more patients with poor collaterals who reperfused well (TICI 2B-3) had good outcomes compared to those who had poor reperfusion (TICI 0–2A), [p=0.017]. Patients with good collateral scores showed a trend for higher rates of good functional outcome with good reperfusion compared to those that had poor reperfusion (p=0.11). In addition, there was no difference in the rate of good functional outcome with good reperfusion in the patients with poor collaterals versus those with good collaterals (p=1.0). The odds ratio (OR) for a 90 day good functional outcome with good reperfusion in those patients with poor collaterals was 12.0 (95% CI, 1.6–98). In the patients with good collaterals, the OR for good functional outcome at 90 days with good reperfusion was 4.7 (0.8–26); difference between ORs not significant (p=0.47).

The time from the end of the baseline MRI to reperfusion was correlated with the collateral score and there was no association across the range of collateral scores (p=0.477). In a dichotomous analysis there was no difference seen between the time from the end of the MRI to reperfusion for patients with poor collateral scores (median time 2.6 hours, IQR 1.8–3.3) versus those with good collateral scores (median time 2.5 hours, IQR 1.9–3.0), [p=0.856]. The interaction of time from the end of MRI to reperfusion with collateral status was also not associated with lesion growth (p=0.952) or good functional outcome (p=0.211).

Target mismatch patients with poor reperfusion (TICI 0–2A) and good reperfusion (TICI 2B-3) were evaluated for hemorrhagic conversion (PH1 and PH2) on the basis of collateral scores. Patients with good reperfusion and poor collateral scores (0–2) had higher rates of parenchymal hematoma development compared to those with good reperfusion and good collateral scores (44% [4/9] versus 26% [5/19]). Similarly, patients with poor reperfusion and poor collateral scores (0–2) had higher rates of parenchymal hematoma development compared to those with poor reperfusion and good collateral scores (41% [9/21] versus 20% [2/10]). However in both cases the differences were not significant (p=0.407 and p=0.425, respectively).

Regression analysis was also performed to understand the how the site of occlusion and the collateral status influenced the baseline NIHSS and perfusion lesion size, as well as the reperfusion status and infarct growth. The rate of TICI 2B-3 reperfusion and Tmax ≥6 sec lesion size were significantly associated with collaterals adjusted for occlusion location (p=0.043 and 0.047 respectively). In addition, there was strong trend for the baseline NIHSS (p=0.088) and some trend for infarct growth (p=0.120) to be associated with collateral status adjusted for occlusion site. At the same time, there was no association between these variables and the occlusion location adjusted for collaterals status. There was no interaction between collateral status and site of occlusion for association with above outcomes.

Discussion

This study demonstrated that there was a relationship between collateral status and the NIHSS stroke scale score at the time of presentation. This is consistent with the finding that the volume of critically hypoperfused tissue (Tmax≥6 sec) from baseline MR perfusion also correlated with the collateral status. A prior study by Bang et al, correlating MR perfusion status and angiographic collateral scores also showed a relationship between the collateral status and the severity of the perfusion deficit.[4] In that study the severity of the perfusion deficit was measured as a ratio between the volume of “penumbral tissue” (measured as Tmax ≥ 4 seconds) and “benign oligemic” tissue (Tmax >2 and < 4 seconds). However, the prior study was not able to show a relationship between collateral status and the penumbral tissue volume using the Tmax ≥ 4 value. More recent work has suggested that Tmax > 6 seconds may better represent critically hypoperfused tissue, [8,9] and this may explain the discrepancy in findings between the two studies.

When we evaluated infarct growth in patients with poor versus good collaterals we found that patients with poor collaterals who did not reperfuse (TICI 0–2A) suffered more infarct growth than those with good collaterals who did not reperfuse. Conversely, infarct growth was not significantly different between those with good and poor collaterals when there was good reperfusion (TICI 2B-3). Bang et al also evaluated infarct growth relative to revascularization in patients with good and poor collaterals. [5] Unlike our results, they found that the patients with poor collaterals and good revascularization had the greatest infarct growth and that it was greater than the growth seen in patients with poor collaterals who did not achieve revascularization. They also reported that in the group with poor collaterals and revascularization there was a higher rate of symptomatic hemorrhagic transformation and suggested that the higher rate of infarct growth may be due to reperfusion injury. Our study

did show a higher incidence of hemorrhagic transformation (PH1 and PH2) in those patients with poor collaterals versus good collaterals, but the difference was not significant. Differences in the study population may explain these different results for infarct growth and hemorrhagic transformation. If for example, the core infarcts were larger in the Bang study they may well have been more prone to reperfusion injury. In addition, our inability to show that hemorrhagic transformation was significantly greater in patients with poor collaterals may be due to the study size being underpowered to show a difference. Campbell et al have recently used Tmax delay as a surrogate for angiographic collateral grading.[13] Their results suggest that the collateral score may be dynamic. Using the Tmax delay for collateral grading allowed them to make repeated measures of collateral flow and they were able to show that infarct growth was associated with collateral failure.

Our finding that reperfusion success is related to the collateral score is in keeping with the prior results reported by prior studies.[5, 14] Bang et al suggested that this may due to the enhanced delivery of both intrinsic and extrinsic thrombolytics to the occlusion site.[5] All of these studies were performed with first generation thrombectomy devices and it will be of interest to see how newer techniques using devices such as stentrievers, which have much higher rates of revascularization, may influence these results.

We were concerned that the site of occlusion could be a confounding variable which would influence the rate of reperfusion as we saw a difference between the rate of good collaterals based on location. However regression analysis demonstrated that TICI 2B-3 reperfusion was associated with the collateral score even after adjustment for site of occlusion and there was no association between the rate of reperfusion and occlusion location, after adjusting for collateral score.

The 90 day clinical outcome results are similar to the infarct growth results seen for patients with good versus poor collaterals. Those patients with poor collaterals who have TICI 2B-3 reperfusion did significantly better than those who did not reperfuse and the odds ratio for good outcome in this group, 12.0 (95% CI, 1.6–98), suggests that there is strong association between reperfusion and good outcome in this group. Patients with good collaterals showed a trend for better outcomes with good reperfusion versus poor reperfusion, odds ratio 4.7 (0.8–26). The smaller odds ratio in this group could imply that patients with good collaterals are more likely to have favorable outcomes even if reperfusion does not occur, however a larger data set is needed to explore this possibility in more detail. The data also suggests that if there is a Target Mismatch, patients should be offered endovascular therapy regardless of the collateral score. While the data does show that patients with poorer collaterals were not as likely to reperfuse using the techniques available to endovascular therapists for this study it also shows that these patients had better outcomes if they were reperfused.

In conclusion, we found that angiographic collateral score correlated with the baseline NIHSS score and the volume of hypoperfused tissue (Tmax≥6 sec) prior to endovascular treatment. In addition, the collateral score also correlated with the rate of TICI 2B-3 reperfusion seen in our patients. Those patients with poor collaterals and poor reperfusion had the most infarct growth and were less likely to have good outcome at 90 days. However, we found a strong association between good reperfusion (TICI 2B-3) and good outcome in

the Target mismatch patients with poor collaterals. This suggests that reperfusion therapy may be beneficial for Target mismatch patients, irrespective of collateral score.

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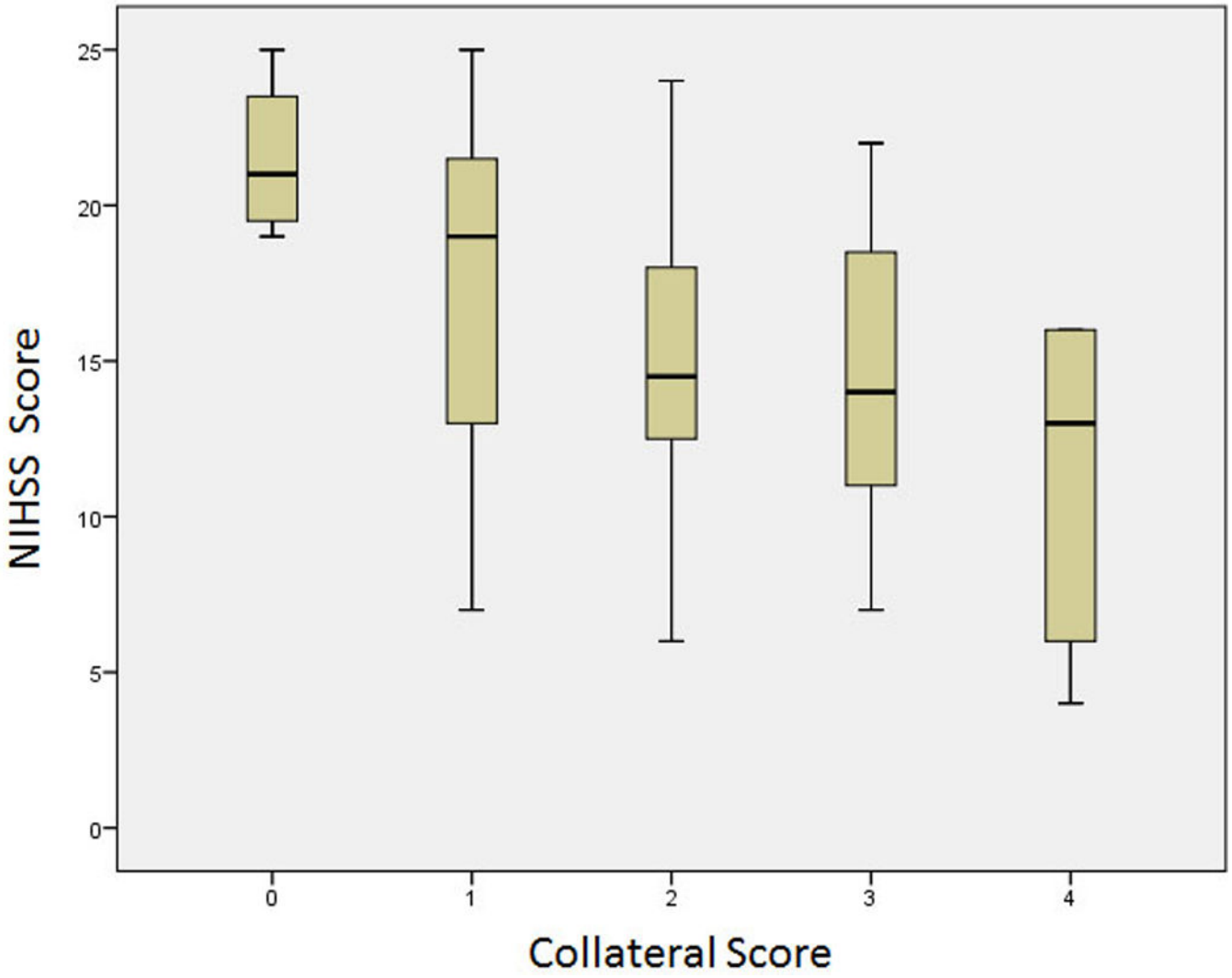

Figure 1.
Box plots showing relationship of NIHSSS to collateral score. Box represents interquartile range, line within box represents median value, and bars show ranges of values.

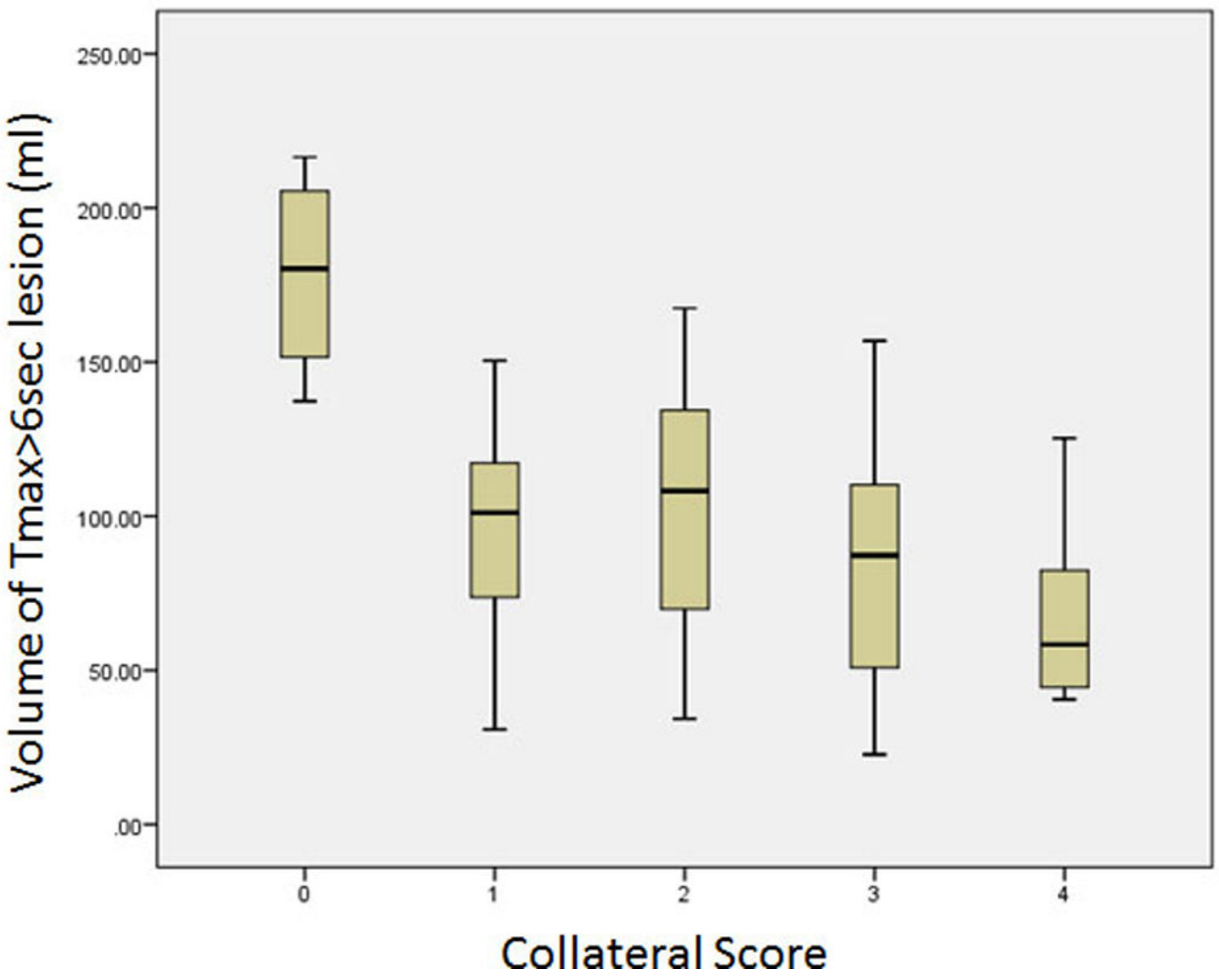

Figure 2.

Box plots showing relationship of volume of tissue with Tmax ≥ 6 seconds to collateral score. Box represents interquartile range, line within box represents median value, and bars show ranges of values.

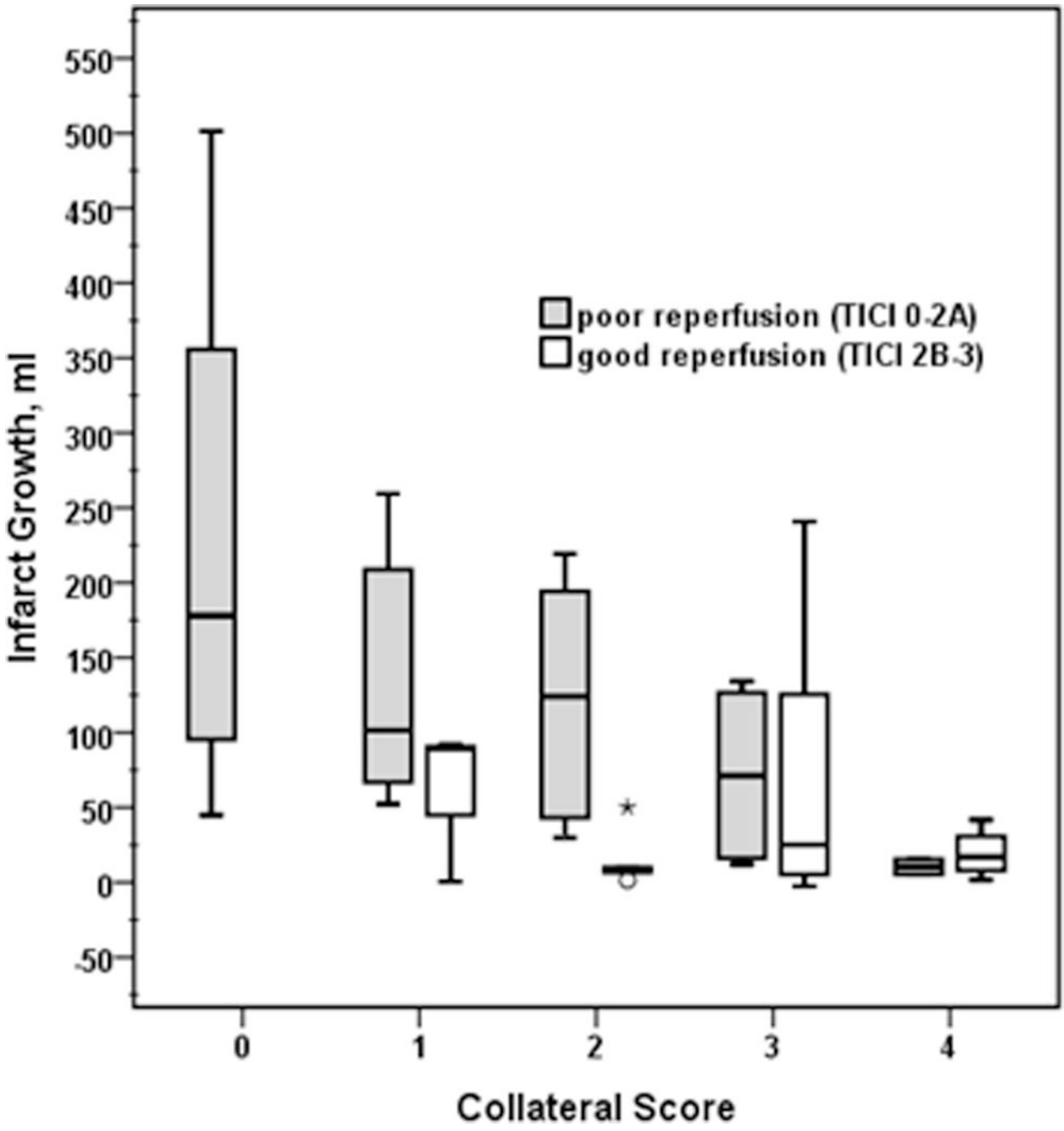

Figure 3.

Box plots showing volume of infarct growth to collateral scores for patients with poor reperfusion (TICI 0–2A) and good reperfusion (TICI 2B-3). Box represents interquartile range (IQR). Line within box represents median value, and bars show ranges of values, circles are values from 1.5–3.0 IQRs and asterisk represents values > 3.0 IQRs.

Table 1

Baseline Characteristics

Characteristic	Entire Group	Poor Collaterals (0–2)	Good Collaterals (3–4)	p- value
Number	60	31	29	
Mean (SD) age – yr	64 (17)	63 (16)	64 (17)	0.874
Female sex – no. (%)	29 (48)	17 (55)	12 (41)	0.316
Hypertension – no. (%)	35 (59)*	18 (60)*	17 (59)	1.0
Diabetes – no. (%)	11 (19)*	3 (10)*	8 (28)	0.104
Hyperlipidemia – no. (%)	27 (46)*	13 (43)*	14 (48)	0.796
Atrial fibrillation – no. (%)	20 (34)*	8 (27)*	12 (41)	0.279
Prior stroke/TIA – no. (%)	12 (20)*	9 (30)*	3 (10)	0.104
Median NIHSSS (IQR)	16 (12–20)	18 (13.5–21.5)	14 (10–17)	0.025
Intravenous tPA pretreatment – no. (%)	33 (55)	18 (58)	15 (52)	0.796
Median time (IQR) symptom onset to start of MRI – hrs	4.5 (3.4–5.9)	4.5 (3.2–5.7)	4.7 (3.7–7.3)	0.318
Median time (IQR) symptom onset to femoral puncture – hrs	6.0 (4.7–7.7)	5.7 (4.7–7.0)	6.2 (4.7–8.3)	0.437
Vessel occlusion on angiogram – no. (%)				<0.001
ICA	17 (28)	15 (48)	2 (7)	
MCA	43 (72)	16 (52)	27 (93)	

Table 2

Collateral Score versus TICI Reperfusion

	TICI Reperfusion				
	0	**1**	**2A**	**2B**	**3**
Poor Collateral Score (0–2)	7 (23)*	5(16)	10(32)	5(16)	4(13)
Good Collateral Score (3–4)	3(10)	0(0)	7(24)	12(41)	7(24)

* number of patients (percentile)

Table 3

TMM Patients with Good Functional Outcome at 90 days*

	Poor Collateral Score (0–2)	Good Collateral Score (3–4)	
Poor Reperfusion (TICI 0–2A)	3/18 (17%)+	3/10 (30%)	P=0.63
Good Reperfusion (TICI 2B-3)	5/7 (71%)	10/15(67%)	P=1.0
	P=0.017	P=0.11	

*Good Functional Outcome is mRS 0–2

+Number of patients with mRS 0–2 over total number of patients in group with equivalent collateral and reperfusion scores