

## Studying the Effect of Ischemic Stroke on Corticospinal Tract in Adults Using Serial Tractography

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### Abstract

**Background:** Cerebrovascular ischemia results from insufficient blood flow due to the obstruction of blood vessels in the brain which leads to rapid cellular necrosis [1]. Depending on the affected populations of neurons, serious deficits can manifest.

**Aim of Study:** To investigate the association of diffusion tensor imaging (DTI) metrics of the corticospinal tract (CST) and clinical assessment on motor recovery at 3 months in ischemic stroke patients.

**Material and Methods:** 23 ischemic stroke patients were included in this observational longitudinal study. The patients underwent DTI scanning in the acute and subacute stages of stroke (Within 2 weeks from the time of the initial impairment and after 3 months respectively). Fractional anisotropy ratio (rFA) and mean diffusivity ratio (rMD) between the ipsilesional and contralesional sides were used as DTI metrics. Standard upper extremity Fugl-Meyer assessment (UE-FM) was used to estimate the functional motor outcome at the same time points of the DTI acquisition. Multiple linear regression analysis was used to develop a prediction model in order to associate the motor outcome (UE-FM at 3 months) to DTI and initial motor assessment variables.

**Results:** 23 stroke patients (mean age  $65.70 \pm 8.86$ , 26.1% females) completed the study. rFA was found to show significant positive correlation with the motor score (UE-FM) in the acute stage ( $r=0.486$ ,  $p=.02$ ) and in the subacute stage ( $r=0.681$ ,  $p=.002$ ). No significant correlations were found between the rMD and the motor score at either of the two time points. The multivariate regression model statistically significantly predicted the motor score at 3 months with an adjusted  $R^2$  of .420,  $p=.004$ . However, only rFA at the subacute stage was independently associated with the motor score in this multivariate framework,  $p=.012$ .

**Conclusion:** We found that rFA values along the CST in the acute and subacute stages of ischemic stroke could help predict the outcome of motor impairment in stroke patients. These results will be useful in furthering our understanding of the motor recovery mechanisms in stroke and will facilitate the clinical decision making.

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**Key Words:** Diffusion tensor imaging – Corticospinal tract – Stroke.

### Introduction

**CEREBROVASCULAR** ischemia results from insufficient blood flow due to the obstruction of blood vessels in the brain which leads to rapid cellular necrosis [1]. Depending on the affected populations of neurons, serious deficits can manifest, the most common being related to the motor function [2]. While the brain is capable of repairing itself, this process is highly imperfect, leaving patients with long-lasting impairments affecting their autonomy in everyday life. One of the most crucial questions in stroke research is to predict the motor outcome. It has been shown that the initial severity of a certain deficit correlates positively to its final severity [3]. Nevertheless, there is a poor specificity-sensitivity tradeoff that affects the clinical scales which are used to quantify the residual neurological function.

Recent work has shown that the motor outcome is affected by structural integrity of the corticospinal tract (CST). The CST is the key pathway which transmits voluntary movements [4]. This implies that the integrity of CST is a potential effective biomarker to predict the outcome in stroke patients [5]. Diffusion tensor imaging (DTI) technique is designed specifically to assess the direction as well as the integrity of the axons of brain fibers [6]. This technique is capable of characterizing the diffusion of water in 3D space and provides complementary insights on the integrity of affected and unaffected neuronal populations of white matter bundles such as the CST [7]. DTI could therefore uncover essential biomarkers indicative of the kind of motor outcome patients may expect.

In addition, there is a technique which is derived from DTI that enables three-dimensional visualization of the CST. This is known as diffusion tensor tractography (DTT) which is used to assess the integrity of the CST [8]. Effectiveness of DTT of CSTs for the prediction of residual motor dysfunction of stroke has been investigated by different studies [9,10].

Reliable prediction of the improvement of motor function in individual patients after stroke is complex. Acute determination of upper limb Fugl-Meyer assessment (FMA) has been found to have a good predictive value [11]. However, a significant category of patients have less improvement than predicted. A wide variability also exists when using other techniques such as diffusion tensor imaging (DTI) [12] in prediction of motor recovery in some stroke patients.

In this study, we aim to investigate the combined influence of DTI measures and clinical assessment on motor recovery in ischemic stroke patients. In particular, the question of whether metrics of DTI assessment or clinical motor assessment are more closely related to motor recovery, and which metric is more predictive to the outcome. This will enable better understanding of the complexity of prediction of motor recovery in stroke and help direct the clinicians to the appropriate therapy.

### Material and Methods

23 patients were recruited from Mansoura University Emergency Hospitals and Neurology Department to this study. All imaging and clinical data were obtained in Mansoura University Hospitals from December 2014 to January 2016. The study protocol was approved by the Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Mansoura University. Participation was entirely voluntary. Informed consent has been acquired from study participants through which the study participants have confirmed their willingness to participate in the research after being informed of the research protocol.

#### *Eligibility criteria:*

*Inclusion criteria included the following:* MRI-demonstrated or CT-demonstrated ischemic stroke, having the first onset within the last 2 weeks prior to recruitment, having the first unilateral ischemic stroke, and follow-up MRI access at 3 months post-stroke.

*Exclusion criteria included the following:* The reoccurrence of stroke before the follow-up at three months, and patients with any known contraindi-

cation to MRI. Vitaly unstable patients and those with terminal illnesses were also excluded.

#### *Study design:*

A prospective longitudinal observational study design was used in this research in which ischemic stroke participants were assessed at two time points: TP 1. Within 2 weeks from the time of the initial impairment (Acute Stage), and TP2. Follow-up after 3 months (Subacute Stage). The assessments included MRI scanning and motor assessments performed at each time point.

#### *Clinical evaluation:*

At each of the two time points, a trained clinician did an evaluation of motor function for the patients to quantify both the global active movement range and the synergies of proximal and distal muscles. The upper extremity Fugl-Meyer (UE-FM) scale was used [13]. The UE-FM scale contains 33 items scored from 0 to 2 (range of total scores 0-66). The higher the scores, the less the impairment. This is a standardised and validated test and is commonly used in clinical assessment of motor impairment in stroke patients.

#### *DTI data acquisition:*

Imaging data was acquired on a 1.5 Tesla, Ingenia MR system (Philips Healthcare, The Netherlands) with 8-channel head coil using typical DWI sequences as well as a DTI protocol. The following DWI sequences were used: (1) an averaged 3-direction DWI ( $b=1000\text{s/mm}^2$ ,  $TR=11700\text{ms}$ ,  $TE=72.3\text{ms}$ , matrix size= $256\times 256$ , slice number=48, voxel size= $0.94\times 0.94\times 3\text{mm}$ ) and (2) a 30-direction DWI (2  $b=0\text{s/mm}^2$  images followed by 30 non-collinear diffusion-encoding gradients at  $b=1000\text{s/mm}^2$ ,  $TR=12000\text{ms}$ ,  $TE=82.3\text{ms}$ , matrix size= $256\times 256$ , slice number=44, voxel size =  $1.09\times 1.09\times 3\text{mm}^3$ ).

#### *Image analysis:*

FSL software v.5.0.8 (FMRIB software library) was used for preprocessing of DTI datasets including brain extraction, the removal of eddy current-induced image distortions and motion artifacts. We adopted fractional anisotropy (rFA) ratio and mean diffusivity (rMD) ratio as DTT parameters. The rFA was determined using a definition of the ratio between ipsilesional FA and contralesional FA ( $\text{FA}_{\text{ipsilesional}}/\text{FA}_{\text{contralesional}}$ ). Likewise, the rMD was defined as the MD value of the affected CST divided by the MD value of the unaffected CST.

Using DTIFIT tool, MD and FA volumes were assessed for every subject. FSL's BedpostX and ProbTrackX tools were used with default param-

ters: 2-fiber model per voxel, 5000 probabilistic streamlines for each tract with a fixed separation distance of 0.5mm between successive points.

*Statistical analysis:*

For descriptive statistics, nominal and categorical variables were presented as absolute numbers and percentages, and continuous variables were summarised as mean with standard deviation (if normally distributed) or as median with range (if not normally distributed). The paired *t*-test (if data is normally distributed) or Mann-Whitney U test (if data is not normally distributed) was used to compare radiological and clinical values in the acute stage (TP 1) with values 3 months after stroke (TP2). Bivariable correlations between DTI measurements (1 measurement at a time) and UE-FM neurological grade were assessed using either-Pearson or Spearman correlation analysis depending on the distribution of the data.

The primary outcome variable was the UE-FM scale at 3 months. Multiple linear regression analysis was used to test the predictive value and the amount of variance ( $R^2$ ) of several variables with regard to the 3-month UE-FM score. The regression model included the following variables: The UE-FM score at baseline, rFA at baseline, rMD at baseline, rFA at follow-up and rMD at follow-up. Age and sex were corrected in the model. *p*-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS (version 25).

**Results**

*Characteristics of participants:*

23 stroke patients (mean age  $65.70 \pm 8.86$ , 26.1% females) participated in the study. Demographic

information and clinical characteristics of the participants are detailed in (Table 1).

*MRI evaluation of ischemic lesions:*

14/23 (60.9%) patients exhibited right hemisphere lesions and 9/23 (39.1%) exhibited left hemisphere lesions. The lesions were broadly distributed within the supratentorial part of the CST pathway. At the time of admission, the CST integrity was disrupted in 19 cases and preserved in 4 cases, while after 3 months 6 cases revealed intact CST.

(Table 2) indicates the changes over time in the rFA and rMD values. Fig. (1) demonstrates the DTI results of CST reconstruction in one of the cases.

Table (1): Demographics and clinical data of participants.

N=23	
Age (yrs)	65.70±8.86
Gender (% , Female)	26.1%
Lesion side (% , Right)	60.9%
Handedness (% , Right)	78.3%
UE-FM - TP1	32.43±19.79
UE-FM - TP2	44.30±16.81
Days after stroke - TP 1	4.70±1.64
Days after stroke - TP2	73.74±6.39
<i>Risk factors:</i>	
Hypertension (%)	69.6%
Coronary artery disease (%)	17.4%
Diabetes (%)	56.5%
Smoking (%)	43.5%

Table (2): rFA and rMD values of the CST in the acute and subacute stages.

	Acute stage TP 1	Subacute stage TP2	<i>p</i>
rFA	0.74±0.11	0.90±0.06	<.005
rMD	1.01±0.09	1.17±0.11	.728

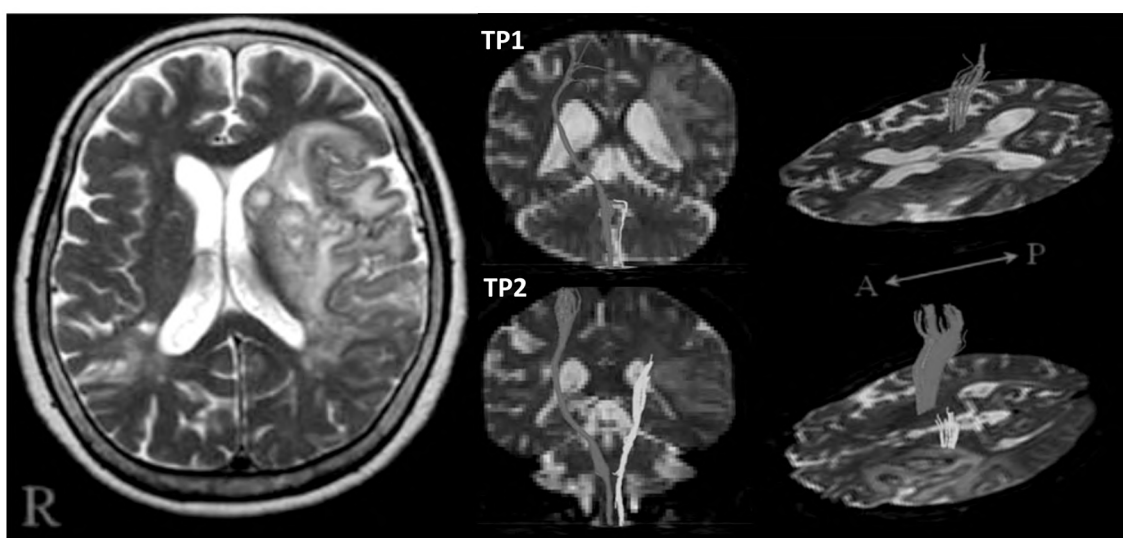


Fig. (1): Results of a representative case from the patients’ dataset. T2WI shows the largest area of the lesion location. Results of CST reconstruction in the acute stage (TP1) and in the subacute stage (TP2) are shown.

We examined correlations between rFA and the upper extremity motor function 3 months after stroke onset at the two time points. The rFA were found to show significant positive correlation with the motor score in the acute stage TP 1 ( $r=0.486, p=.02$ ) and in the subacute stage TP-2 ( $r=0.681, p=.002$ ). Fig. (2) demonstrates correlations of the rFA metric of the CST and the motor score. On the other hand, no significant correlations were found between the rMD and the motor score at either of the two time points.

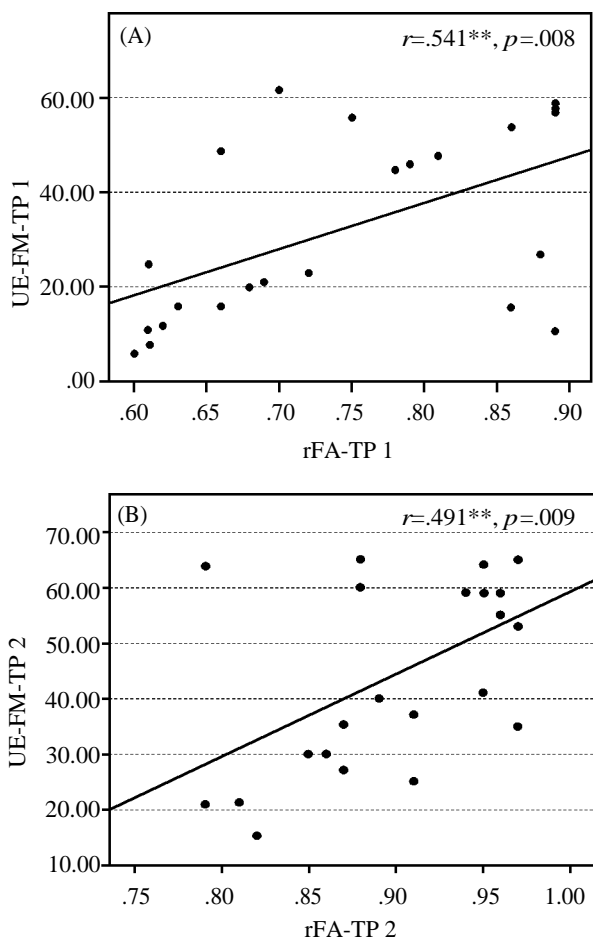


Fig. (2): Correlations between rFA values and the motor outcome scores in the acute (A) and subacute (B) stages.

#### Multiple regression analysis for motor improvement prediction.

We investigated whether DTI and clinical markers were independently predictive of motor function (UE-FM) at 3 months while accounting for age and gender.

In the initial univariate analysis, the significant factors related to the motor function included rFA at the acute stage (TP-1), rFA at the subacute stage (TP-2) and the UE-FM motor score at the acute stage (TP1). rMD at either of the time points did not show

significant value in this univariate analysis. The significant factors were then fed into the multivariate linear regression analysis as predictors. The overall model statistically significantly predicted the motor score at 3 months with an adjusted  $R^2$  of .420,  $p=.004$ . However, only rFA at the subacute stage (rFA-TP2) was independently associated with the motor score in this multivariate framework,  $p=.012$  (Table 3).

Table (3): Multiple regression modelling for predicting 3-months UE-FM motor score.

Model	$r$	$r$ Square	Adjusted $r$ Square	Sig.
1	.706a	.499	.420	.004

a. Predictors: (Constant), rFA-TP2, UE-FM-TP1, rFA-TP 1.

Model	Unstand-ardized B	Coeffi-cients Std. Error	Standa-rdized Coeffi-cients Beta	$t$	Sig.
1 (Constant)	-169.152	58.756		-2.879	.010
UE-FM-TP 1	-.165	.178	-.195	-.927	.365
rFA-TP1	-42.152	51.372	-.275	-.821	.422
rFA-TP2	278.178	100.002	1.042	2.782	.012

a. Dependent Variable: UE-FM-TP 2

## Discussion

The aim of this study was to provide more details of motor prognosis following ischaemic stroke using DTI. In this study, we show that a combination of DTI measures as well as neurological motor assessment can be used to predict the outcome of motor function at 3 months after stroke. FA ratios between the affected and unaffected CST at both acute and subacute stages were found to show positive correlation with assessments of motor outcome. In addition, motor recovery in the upper extremity at 3 months after stroke onset was independently predicted by the rFA in the subacute stage in a multivariate regression model. In contrast, rMD values at either of the two time points were not found to be independent predictors of the motor outcome at 3 months after stroke.

FA values represent the degree of damage to neuronal microstructure and its directionality in a neural tract. This damage to the neuronal integrity can reduce FA value [14] which explains the observed correlation between FA ratios and motor function. The detected correlation depicts a positive association between the motor function on the affected side in patients with the degree of CST injury. This observation in the findings of our study is in agreement with the conclusions of previous research [14-16].

We found the strength of the significant positive correlation between rFA values and the motor function assessment in the subacute stage to be higher than correlation in the acute stage. This observation may suggest that motor recovery in patients with stroke is associated with residual ipsilateral CST integrity rather than initial impairment.

Regarding limitations of the present study, firstly, the sample size was small. However, the longitudinal study design with 2 repeated measures may have compensated for this limitation. Secondly, no restrictions were applied on the age of participant and thus age-related brain degeneration cannot be ruled out in the results. A larger subject-pool with categorisation would be essential to provide more accurate predictions of prognosis among different age groups. Despite the above limitations, our results have shown the importance of assessing ipsilateral CST integrity for goalsetting during stroke rehabilitation.

Furthermore, we emphasize that the DTI has limitations which have to be considered when it comes to results interpretation [17]. In particular, DTI may underestimate fiber tracts as the technique for fiber tracking is operator-dependent. In addition, the original DTI signal-to-noise ratio may have affected the data of fiber-tracking, if the original image had a poor quality and this could have undermined the reliability of fiber tracking. In potential future studies, combining DTI with other techniques e.g. functional MRI can prove to be necessary to elucidate the mechanisms of rehabilitation neural function further.

In summary, results of this study demonstrate the predictive value of DTI metrics of CST with regard to the motor outcome at the subacute stage after stroke onset. DTI allows prediction of prognosis by obtaining rFA values via tractography. This suggests that early and subacute DTI evaluations for the CST could be useful for prediction of motor outcomes of affected extremities in stroke patients which will facilitate clinical decision making.

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## دراسة تأثير السكتة الدماغية على الالياف القشرية النخاعية في البالغين باستخدام التصوير المتتابع للالياف العصبية

الهدف من البحث: التحقيق فى إرتباط مقاييس التصوير الموتر للإنتشار (DTI) المتعلق بالقناة النخاعية مع التقييم السريرى لإستعادة الحركة لدى مرضى السكتة الدماغية.

المواد والأساليب: تم فحص ٢٣ مريضاً من مرضى السكتة الدماغية. تم إستخدام مقاييس التصوير الموتر للإنتشار على جميع المرضى فى المراحل الحرجة وتحت الحرجة من السكتة الدماغية (أى فى غضون أسبوعين من وقت الضعف الأولى ولمدة ثلاثة أشهر على التوالى). تم إستخدام نسبة التباين الجزئى (rFA) ومتوسط نسبة الإنتشار (rMD) كما تم إستخدام التقييم القياسى للطرف العلوى (FMA-UE) لتقدير النتيجة الحركية الوظيفية فى نفس النقاط الزمنية لإكتساب التصوير الموتر للإنتشار. أيضاً تم إستخدام تحليل الإنحدار الخطى المتعدد لربط النتيجة الحركية بالتصوير الموتر للإنتشار ومتغيرات التقييم الحركى الأولى.

النتائج: أتم ثلاثة وعشرون مريضاً من مرضى السكتة الدماغية الدراسة (متوسط العمر ٦٥.٧، ١، ٢٦.١٪ إناث). تم العثور على نسبة التباين الجزئى الذى أظهر إرتباط إيجابى مع درجة النتيجة الحركية الوظيفية فى المرحلة الحرجة ( $r=0.486, p=0.02$ ) وفى المرحلة قبل الحرجة ( $r=0.681, p=0.002$ ). كما أنه لم يتم العثور على إرتباطات ذات دلالة إحصائية بين متوسط نسبة الإنتشار ودرجة المحرك فى أى من النقطتين الزمنيتين. ومن الجدير بالذكر أن نموذج الإنحدار متعدد المتغيرات قد تنبأ إحصائياً بنتيجة الفحص الاكلينيكي عند ٣ أشهر مع معامل الارتباط الثنائى.

الملخص: تم التوصل إلى أن إستخدام نسبة التباين الجزئى (rFA) على إمتداد المسار القشرى النخاعى فى المراحل الحرجة وتحت الحرجة من السكتة الدماغية يمكن أن يساعد فى التنبؤ بنتيجة الخلل الوظيفى الحركى. وتعد هذه النتائج مفيدة فى تعزيز فهمنا لآلية التعافى الحركى فى السكتة الدماغية وتسهيل إتخاذ القرارات الإكلينيكية.