# Crítica de artículo científico

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# Breaking with a dogma: persisting diffusion restrictions (pDWI) in follow-up after endovascular treatment for stroke

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1. **ISQUEMIA:**
    1. Transcurso isquemia a un infarto: movimiento de agua del espacio extracelular al compartimento intracelular. Hallazgos: señal t2 normal.
    2. Rotura endotelial con edema vasogénico y aumento total del contenido de agua: Hallazgo señal alta t2. DW identifica el infarto en etapa más precoz (antes del edema vasogénico)

**Agudo: 0-7 días.** DWI alta con ADC bajo.
**Subaguda: 1 a 3 s**: , DWI alta persiste hasta 14 días desde inicio y luego baja. ADC primero se normaliza ( pseudonormalización) y luego señal alta.
**Crónica: 3 s**. DWI variable. Normalmente iso/hipointensa pero dependiendo del efecto T2. ADC alto.

**Las anomalías persistentes de DWI (pDWI) son aquellas que no siguen la línea de tiempo descrita. ESTUDIO busca caracterizar y clasificar las anomalías DWI persistentes para DETERMINAR SU RELEVACIA CLÍNICA.**

# Título y abstract

***Alto ADC y DWI variable, se completa a más tardar 1 mes***

***¿Encontraron excepciones a esta línea de tiempo de cambio en la señal DWI?***

***Incertidumbres en el manejo clínico posterior del paciente***

- Prospectivo. Un único centro.
- Trombectomía de gran vaso de circulación anterior
- DW agudo y seguimiento entre 3-12 m

**Las anomalías persistentes de DWI (pDWI)**


**ABSTRACT**

**Background** Post-stroke diffusion weighted imaging (DWI) signal transformation of the infarct core, which results in high apparent diffusion coefficient (ADC) values and variable DWI signal intensity, is completed no later than 1 month after onset of ischemia. We observed frequent exceptions to this timeline of change in DWI signal, which led to uncertainties in further clinical patient management.

**Methods** A prospective single-center study of patients treated with mechanical thrombectomy of a large vessel occlusion in the anterior circulation was conducted. Patients received high-resolution MRI at 3T, including DWI, in the acute post-stroke phase and in the follow-up after 3–12 months.

**Results** Overall, 78 patients (45 men) of mean age 63.6 years were evaluated. We identified persisting or new diffusion restriction in 29 of the 78 patients (37.2%) on follow-up imaging. Diffusion restrictions in a different location from the infarct core, representing new (sub-)acute ischemia, were observed in four patients (5.1%). Smaller areas of persisting diffusion restriction (pDWI lesions with high DWI signal and reduced ADC values) within the former infarct core were observed in 25 patients (32.1%) without clinical evidence of recurrent stroke, but with worse outcome scores at follow-up compared with patients without pDWI lesions. The presence of pDWI lesions is associated with a large primary infarct core (multivariate regression OR 1.03 (95% CI 1.01 to 1.05); $p<0.01$), mediating the relationship between pDWI lesions and clinical outcome.

**Conclusion** Smaller foci of persisting diffusion restriction (pDWI lesions) in the follow-up after endovascular treatment for stroke are frequent and likely represent a slowed ADC signal progression within a formerly large infarct core.

- **Muestra 78 pacientes (45 hombres)**

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- ***37.2%:*** **persistencia o nueva restricción de difusión.**
- ***5.1%:*** **Restricción DW en otro sitio diferente al núcleo infartado/isquemia subaguda nueva.**

- ***32.1%:*** **Áreas más pequeñas de restricción con señal DWI alta y valores ADC reducidos) dentro del núcleo del infarto anterior. Esto se da en infarto grande …**

**Focos pequeños de restricción en seguimiento probablemente representan una progresión más lenta de la señal ADC dentro de un núcleo de infarto grande.**


## ABSTRACT

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# Introducción

## INTRODUCTION

Diffusion weighted imaging (DWI) is used to differentiate ischemic stroke from a transient ischemic attack[1] or other differential diagnoses, to help categorize stroke etiology based on infarct distribution, and to predict outcome[2] or risk of secondary infarct bleeding.[3 4]

In acute ischemic stroke (0–7 days from onset), DWI shows a high signal with reduced apparent diffusion coefficient (ADC) values in the affected brain parenchyma.[5] In the subacute stage, usually defined as the period 1–3 weeks after onset, a high DWI signal persists up to 14 days after onset and later diminishes while ADC first normalizes to values of healthy brain tissue (frequently referred to as pseudonormalization) and later increases to a high signal intensity. In the chronic stage, beginning 3 weeks after onset, the DWI signal is variable but usually isointense to hypointense depending on the underlying T2 signal and the ADC values are high.[5] If the underlying T2 relaxation is sufficiently prolonged, the resulting DWI signal may appear high even though the corresponding ADC values are also high, an effect known as 'T2 shine-through'.[6]

In an ongoing clinical study at our comprehensive stroke center, patients who undergo endovascular therapy (EVT) for ischemic stroke receive regular follow-up MRI 3–12 months after discharge. Persisting DWI abnormalities (pDWIs) that did not follow the above described signal change timeline were frequently observed without new clinical symptoms, often leading to insecurities in radiological assessment and clinical management. This raises

In this study we sought to characterize and classify the observed persisting DWI abnormalities with the aim of determining their clinical relevance.

# Método

## METHODS

In a prospective single-center study, patients who underwent EVT for ischemic stroke were followed up longitudinally. As the primary end point, clinical and imaging characteristics were collected at 3-month follow-up. If there were any abnormalities, further examinations were sometimes carried out at 12 months. Imaging studies performed at 3–12 months are part of the study design and performed outside of clinical routine solely for research purposes. Prospective acquired clinical and imaging data were retrospectively analyzed.

***Estudio prospectivo de un solo centro, con seguimiento longitudinal***

**Protocolo de estudio de la RM**

**Los datos clínicos y de imágenes adquiridos prospectivamente se analizaron retrospectivamente.**

## Study population

The study cohort consisted of 589 patients with stroke who were treated with mechanical thrombectomy in a single comprehensive stroke center between October 2018 and February 2021. Ninety-seven patients underwent both MRI in the acute post-stroke stage (median 3 days after mechanical thrombectomy) and a second MRI in the 3-month follow-up period with neurological examination. Nine patients were excluded due to MRI of insufficient quality in the acute post-stroke stage including fluid-attenuated inversion recovery (FLAIR) and DWI, seven patients were excluded due to EVT of a large vessel occlusion of the posterior circulation, and three patients were excluded due to susceptibility-induced DWI artifacts at the 3-month follow-up (see online supplemental file 1 for an example of susceptibility-induced DWI artefacts). The final study cohort therefore consisted of 78 patients (see online supplemental figure S2 for a summary of the subject inclusion process). From the subgroup of patients with pDWI lesions, further follow-up at 12 months was performed for patients with imaging and clinical examination.

Angiographic and clinical data at the acute stage were prospectively collected within a registry. The time interval to reperfusion is defined as the time difference between symptom onset or time of recognition to reperfusion time. The success of reperfusion, measured by the expanded Treatment in Cerebral Ischemia (eTICI) score,[7] was determined by two experienced neurointerventionalists in consensus. Successful recanalization was defined as eTICI ≥2b and complete recanalization as eTICI 2c–3.

The clinical data at admission (pretreatment), at discharge (post-treatment) and at follow-up, including the National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score, were assessed by certified neurologists. Substantial neurological improvement was defined as the difference between discharge and follow-up NIHSS score of ≥8 or follow-up NIHSS score of ≤1. The mRS score was used to measure disability at follow-up, with a good clinical outcome defined as mRS score of ≤2.

Stroke pathogenesis was determined according to the international TOAST (Trial of ORG 10172 in Acute Stroke Treatment)[8] classification based on the diagnostic and clinical information available for each patient.

The peak leucocyte counts during the acute stroke phase of all patients (during their hospital stay, maximum of 11 days after EVT) were retrospectively assessed from the routine laboratory measurements.

***Estudio prospectivo de un solo centro, con seguimiento longitudinal***

La cohorte de estudio  589 pacientes con accidente cerebrovascular tratados con trombectomía mecánica entre 2018 -2021.

- **97 pacientes** . ***1º RM*** en etapa aguda (mediana de 3 días del tratamiento trombectomía ). ***2º RM*** en el período de seguimiento de 3 meses +  examen neurológico.

  12 excluídos por baja calidad RM y 7 por ACV en circ post.

**Cohorte final del estudio consistió en 78 pacientes**

**Del subgrupo de pacientes con lesiones pDWI, se realizó un seguimiento adicional a los 12 meses para los pacientes con imágenes y examen clínico.**

1. Etapa aguda: **datos angiográficos y clínicos se recolectaron prospectivamente** .

- El éxito de la reperfusión, medido por puntuación ampliada del Tratamiento en Isquemia (eTICI).
  - Exitosa TICI ≥2b y completa TICI 2c-3.

**Consenso de por dos neurointervencionistas experimentados**

- Datos clínicos en ingreso y seguimiento: NIHSS, escala de Rankin modificada
  - La mejoría neurológica sustancial si diferencia NIHSS entre el postratamiento y el seguimiento fue de > 8 o NIHSS de seguimiento de ≤1. Discapacidad medido por Rankin: buen resultado si ≤2.
  - **Consenso de neurólogos**

**Recuento máximo de leucocitos durante la fase aguda del ictus se evaluaron retrospectivamente**

## Imaging analysis

All imaging data were evaluated by a neuroradiologist with more than 4 years of experience (MTB). Patients with diffusion restrictions (high signal on DWI and reduced ADC values) at follow-up imaging were selected and signal changes were compared with imaging of the acute stage for the same patient.

The imaging data (isotropic DWI and 3D FLAIR images from the acute stage and during follow-up) of all patients were processed using BrainLab Elements Virtual iMRI (BrainLab, Feldkirchen, Germany). Ischemic and stroke lesions were semi-automatically segmented (using the applications Image Fusion v4.0, Smartbrush v2.6/3.0, Object Management v1.1). Lesion volumes were extracted.

***«Segmentación robusta basada en aprendizaje profundo de glioblastoma en exploraciones clínicas de resonancia magnética de rutina utilizando entrenamiento disperso» 2020***

***«Segmentación automática de anomalías difusas de la sustancia blanca en imágenes de RM del cerebro potenciadas en T2 mediante aprendizaje profundo en RN muy prematuros» 2021***

Asociación de varias variables iniciales con la presencia de lesiones DWI persistentes (pDWI).

ANÁLSIS DE REGRESIÓN MÚLTIPLES

## Statistical analyses

In a univariate non-adjusted analysis, various baseline variables were tested for their association with the presence of persisting DWI (pDWI) lesions. Independent sample t-tests were used for parametric variables, Wilcoxon rank-sum tests for non-parametric variables, and the Fisher exact test for dichotomous categorical variables. A multivariate logistic regression model was performed as a second step.

In a mediation model, the presence of pDWI lesions was entered as the causal variable, the NIHSS score at follow-up as the outcome variable, and the ischemic volume as the mediator variable. Covariates such as age, sex, IV thrombolysis, time interval, reperfusion success (complete vs incomplete), leukocyte count, and follow-up interval were considered. Path coefficients were estimated using non-standardized regression coefficients of multiple regression analyses. The statistical significance of the indirect pathway, reflecting the impact of mediation, was evaluated using a non-parametric bootstrap approach with 5000 replication samples to obtain a 95% CI.[9 10]

All statistical analyses were performed using SPSS Statistics version 28.0 (IBM, Armonk, New York, USA).

# Resultado

| Variable | DWI pDWI lesions (n=25) | No DWI (n=49) | pDWI vs no DWI) |
|---|---|---|---|
| Age, years, mean (SD) | 66,1 (14,1) | 61.3 (14.8) | 0.2 |
| Sex (F/M), n | 12/13 | 18/31 | 0.4 |
| IV thrombolysis, n (%) | 14 (56%) | 33 (67.3%) | 0.3 |
| Leucocyte max count (blood), mean (SD)* | 10.7 (2.7) | 10.9 (3.9) | 0.8 |
| Time interval to reperfusion, min, median (IQR)† | 209 (180–280) | 219 (179–257) | 0.9 |
| eTICI score post recanalization, n for 0–2a/2b/2c–3 | 0/7/18 | 0/14/35 | 0.3 |
| Complete reperfusion (eTICI 2c/3), n (%) | 18 (72%) | 35 (71.4%) | 0.9 |
| Follow-up interval, days, median (IQR)‡ | 98 (92–104) | 98 (94–103) | 0.7 |
| Primary infarct volume, mL, median (IQR) | 35.1 (21.2–182.1) | 11.4 (2.93–92.5) | **<0.001** |
| Lesion at follow-up, mL, median (IQR) | 24.0 (9.53–153.8) | 3.7 (0.77–60.0) | **<0.001** |
| Lesion decrease, %, median (IQR)§ | 50.31 (36.9–81.2) | 64.0 (49.3–98.7) | **0.007** |
| NIHSS, median (IQR) | | | |
| Pretreatment | 14 (10–15.5) | 8 (5–13) | **0.008** |
| Post-treatment (at discharge) | 3 (1–7) | 1 (0–2.5) | **0.01** |
| At follow-up | 1 (0.5–4.5) | 0 (0–1) | **0.003** |
| Substantial neurological improvement (discharge to follow-up), n (%) | 13 (52%) | 39 (79.6%) | **0.014** |
| mRS score at follow-up, median (IQR) | 1 (1–2.5) | 1 (1–2) | 0.09 |
| Good clinical outcome at follow-up (mRS 0–2), n (%) | 19 (76%) | 42 (85.7%) | 0.3 |
| TOAST (1/2/4/5), n | 6/10/3/6 | 15/13/7/14 | 0.7 |

*pDWI en áreas de materia gris.*

*No necrosis laminar en pDWI*

*No se encontró evidencia de reoclusión en pDWI .*

- **Modelo de regresión logística multivariante variable, solamente el volumen isquémico tuvo pDWI.**
- **pDWI mayor volumen del infarto primario que el grupo sin DWI (mediana (RIC) 35,1 (21,2–182,1) ml frente a 11,4 (2,93–92,5) ml, p<0,001**
- **Rango de volúmenes de infarto primario para lesiones pDWI fue de 5,4 a 188,7 ml.**

**En la observación descriptiva de los 2 casos con examen de seguimiento prolongado (12 m ): pDWI eran persistentes con ligera reducción de volumen y una señal ADC creciente en las imágenes hasta 12 meses después**

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1. pDWI tuvo NIHSS medianas (IQR) más altas que el grupo no DWI.

**Utilizando el volumen isquémico como variable mediadora, el efecto de las lesiones pDWI sobre el resultado clínico perdió su significación estadística (p=0,11).**

**¡Volumen isquémico media la relación entre las lesiones pDWI y el resultado clínico!**

**25 pacientes pDWi. Ninguno presentó ningún síntoma clínico nuevo y la puntuación NIHSS no empeoró**

**(Menor mejora neurológica sustancial entre el alta y el seguimiento significativamente en grupo pDWI)**

# Discusión

# 1. pDWi muestra señales similares a isquemia aguda

**2. pDWI puede llevar a intensificación de tratamiento . Pero correcta exploración neurológica puede evitarlo sin empeoramiento clínico**

**pDWI más allá de 1 mes , incluso 3 meses después de un accidente cerebrovascular agudo**

**¿Causas?**

- Mayor grado y persistencia de inflamación posterior al accidente cerebrovascular, necrosis y eliminación celular (compatible con infarto grande)
- La necrosis laminar o el sangrado
- Lesiones endoteliales que fueron tratados con trombectomía
- Excitación neuronal anormal de la sustancia gris supv
- **Microinfartos silenciosos**

# Conclusión y limitaciones

- Se observaron (pDWI) en el 32,1 % de los pacientes. El sello distintivo de un accidente cerebrovascular recurrente claro es la difusión restringida lejos del infarto original

- Examen neurológico completo para excluir la recurrencia del accidente cerebrovascular sintomático , para evitar mayor escalamiento diagnóstico y terapéutico.

- Microinfarto vs pDWi

# Puntos a favor

- Recolección de datos  prospectivamente
- Factores de confusión.
- Cuantificación de las pérdidas.
- Tiene en cuenta el sesgo de validación ya que define el protocolo a seguir de forma prospectiva , realizando RM  y la pauta a seguir en todos.
- Especifica los métodos de seguimiento.
- Buen análisis  estadístico

Estudio observacional y analítico

BASANDOME EN EL ESTROBE PARA LA VALORACIÓN DE ESTUDIOS OBSERVACIONALES

# Limitación del estudio

- **Tanto título como hipótesis poco desarrollada**
- **¿Qué paso con el resto de la cohorte?--- 587 a 78 pacientes.**
- **Muy pocos casos de seguimiento prolongado (2): limita análisis.**
- **RM solo  a los 3 meses y a los 12 m solo en pDWi**
- **¿Excluimos pDWi de otra localización?**
- **Todos los pacientes sometidos a trombectomía:  sesgo?? ()**
- **pDWi también se dieron en infartos  pequeños  ( a partir de 5,4 ml) ¿NO solamente es el volumen de infarto?.**
- **Falta de correlación histopatológica: fisiopatología hipotética.**
- **No es multicéntrico, escasa representación de la población.**
- **Explique cómo se determinó el tamaño muestral (parámetros, justificación…)**
- **Estado actual de investigaciones .**
- **Defina claramente todas las variables: de respuesta, exposiciones, predictoras, confusoras y modificadoras del efecto.** SOLAMENTE CONFUSORAS EL SEXO Y POCO MAS, Y EL TRATAMIENTO DE BASE??
- **Características de los participantes del estudio : Tto, demencias…**
- **Niebla:** Calcula la media de palabras por frase. Regular