The Value of Transcranial Doppler Sonography in Hyperperfusion Syndrome after Carotid Artery Stenting: A Nationwide Prospective Study

Francisco Moniche, Irene Escudero-Martínez, Fernando Mancha, Alejandro Tomasello, Marc Ribó, Fernando Delgado-Acosta, Juán José Ochoa, Joaquín Gil, Rosario Gil, Montserrat González-Delgado, Eduardo Murias, Alain Luna, Alberto Gil, Sonia Mosteiro, María Dolores Fernández-Couto, Luis Fernández de Alarcón, José M. Ramírez-Moreno, Joaquín Zamarro, Guillermo Parrilla, José L. Caniego, Gustavo Zapata-Wainberg, Andrés González-Mandly, José A. de las Heras, Luis López-Mesonero, Joaquin Ortega, Juan F. Arenillas, Ernesto García, Pedro P. Alcázar, Elena Zapata-Arriaza, Asier de Albóniga-Chindurza, Juan Antonio Cabezas, Pilar Algaba, Aurelio Cayuela, Joan Montané, Alejandro González García

Department of Neurology, Virgen del Rocio University Hospital, Sevilla, Spain
Neurovascular Research Laboratory, Institute of Biomedicine of Seville-IBiS, Sevilla, Spain
Interventional Neuroradiology, Department of Radiology, Vall d’Hebron Hospital, Barcelona, Spain
Department of Neurology, Vall d’Hebron Hospital, Barcelona, Spain
Interventional Neuroradiology, Department of Radiology, Reina Sofia Hospital, Córdoba, Spain
Department of Neurology, Reina Sofia Hospital, Córdoba, Spain
Interventional Neuroradiology, Department of Radiology, Clínico de Valencia Hospital, Valencia, Spain
Department of Neurology, Valencia Clinical Hospital, Valencia, Spain
Department of Neurology, Central de Asturias Hospital, Oviedo, Spain
Interventional Neuroradiology, Department of Radiology, Central de Asturias Hospital, Oviedo, Spain
Department of Neurology, Cruces Hospital, Bilbao, Spain
Interventional Neuroradiology, Department of Radiology, Cruces Hospital, Bilbao, Spain
Interventional Neuroradiology, Department of Radiology, Juan Canalejo Hospital, A Coruña, Spain
Department of Neurology, Juan Canalejo Hospital, A Coruña, Spain
Interventional Neuroradiology, Department of Radiology, Infanta Cristina Hospital, Badajoz, Spain
Department of Neurology, Infanta Cristina Hospital, Badajoz, Spain
Interventional Neuroradiology, Department of Radiology, Virgen de la Arrixaca Hospital, Murcia, Spain
Interventional Neuroradiology, Department of Radiology, Princesa Hospital, Madrid, Spain
Department of Neurology, Princesa Hospital, Madrid, Spain
Interventional Neuroradiology, Department of Radiology, Marques de Valdecilla Hospital, Santander, Spain
Interventional Neuroradiology, Department of Radiology, Salamanca Hospital, Salamanca, Spain
Department of Neurology, Salamanca Hospital, Salamanca, Spain
Interventional Neuroradiology, Department of Radiology, Virgen del Rocio University Hospital, Sevilla, Spain
Department of Neurology, University Clinical Hospital of Valladolid, Valladolid, Spain
Interventional Neuroradiology, Department of Radiology, Virgen de las Nieves Hospital, Granada, Spain
Unit of Clinical Management of Public Health, Prevention and Promotion of Health, Area of Sanitary Management South of Sevilla, Sevilla, Spain
Department of Neurology, Virgen Macarena University Hospital, Sevilla, Spain
Dear Sir:

Cerebral hyperperfusion syndrome (CHS) is a life-threatening complication, defined as a combination of clinical features with evidence of hyperperfusion >100%.1 Hyperperfusion has been reported in 1% to 3% after carotid artery stenting (CAS).1 Although hyperperfusion evidence in those patients with the typical clinical syndrome seems to be a critical aspect of the CHS, the severity of the cerebral perfusion increase that is needed to develop the CHS is not clear.2 Definitions with different degrees of hyperperfusion have been used to diagnose CHS, although the most widely used is an increase in cerebral blood flow of more than 100% compared with baseline values.1 The aim of the study was to validate prospectively the transcranial Doppler (TCD) criteria in diagnosis of CHS after CAS in a nationwide study.

This is a national prospective multicenter study. Inclusion criteria are detailed elsewhere.3 All patients underwent a baseline examination and follow-up was done up to 30 days with strict periprocedural blood pressure control. TCD was done before and 24 hours after CAS. In those patients with clinical-radiological CHS TCD was repeated at symptoms onset. Peak systolic velocity (PSV), pulsatility index (PI), and cerebrovascular reactivity (CVR) in middle cerebral artery (MCA) were measured. CHS was defined as (1) typical CHS clinical features with or without cerebral edema or intracerebral hemorrhage (ICH); (2) alternative diagnoses should be ruled out; and (3) evidence of hyperperfusion. Per protocol, there was no defined cut-off point for CHS diagnosis. CHS was classified as mild (only cephalgia) or moderate-severe (impaired level of consciousness, seizures, neurological deficit, and/or ICH). We used univariate analysis for comparisons (SPSS version 25.0, IBM Co., Armonk, NY, USA; with P<0.05 as statistically significant). Area under the curve (AUC) was calculated to evaluate the accuracy of the increase of PSV for CHS diagnosis. The study was approved by the University Hospital Virgen del Rocio Ethics Committee. All patients signed informed consent forms.

Of 757 patients enrolled in the Hyperperfusion Syndrome Post-carotid ANgloplasty And Stenting (HISPANIAS) study, Table 1. Baseline patient characteristics

| Characteristic                  | Non-CHS (n=537, 96.2%) | CHS (n=21, 3.8%) | P   |
|--------------------------------|------------------------|-----------------|-----|
| Men                            | 444 (82.7)             | 14 (66.7)       | 0.08|
| Age (yr)                       | 71 (63–78)             | 76 (73.5–78)    | 0.01|
| Previous TIA or stroke         | 436 (81.2)             | 20 (95.2)       | 0.14|
| Hypertension                   | 414 (77.8)             | 18 (85.7)       | 0.59|
| Diabetes                       | 205 (38.5)             | 12 (57.1)       | 0.08|
| Hyperlipidemia                 | 332 (62.4)             | 14 (66.7)       | 0.69|
| Ischemic cardiopathy           | 153 (28.9)             | 4 (19)          | 0.33|
| Percentage of stenosis (%)     | 88 (80–95)             | 90 (85–90)      | 0.16|
| Symptomatic stenosis           | 469 (81.4)             | 20 (95.2)       | 0.15|

Values are presented as number (%) or median (interquartile range). CHS, cerebral hyperperfusion syndrome; TIA, transient ischemic attack.

Table 2. TCD data comparison before and after CAS

| Variable                        | Non-CHS (n=537) | CHS (n=21) | P    |
|---------------------------------|-----------------|------------|------|
| **Baseline TCD**                |                 |            |      |
| Diminished vasoreactivity (%)   | 32.6            | 36.8       | 0.69 |
| PSV (cm/sec)                    | 74.0 (62.3–89.9)| 71.4 (50.3–83.2)| 0.23 |
| PI                             | 0.97 (0.8–1.1)  | 0.80 (0.6–1.2)| 0.23 |
| **Post-CAS TCD**                |                 |            |      |
| PSV (cm/sec)                    | 95.0 (76.1–118) | 123.9 (90.6–143.4)| 0.006|
| PI                             | 1.10 (0.99–1.4) | 1.30 (1.1–1.6)| 0.043|
| Increase of PSV (%)             | 22.1 (6.3–47.5) | 73.5 (20–132.1)| <0.001|
| Increase of PI (%)              | 16.9 (0–40.2)   | 46.9 (18.9–83.9)| 0.003|

Values are presented as median (interquartile range). TCD, transcranial Doppler; CAS, carotid artery stenting; CHS, cerebral hyperperfusion syndrome; PSV, peak systolic velocity; PI, pulsatility index.
CAS values, even in those CHS patients with ICH.

In one of the biggest series published, a low positive predictive value of increases of >100% of PSV (8.0%), with 66% of sensitivity was described, concluding that significant increases in MCA velocity did not identify patients at increased risk of suffering CHS. However, this cut-off point of hyperperfusion >100% compared to baseline values for CHS diagnosis would have been underdiagnosed in our study about half of the patients that developed the clinical symptoms and neuroimaging CHS changes and had no evidence of alternative diagnosis.

We could classify TCD changes in four different patterns: (1) “benign hyperperfusion” with >100% in PSV without symptoms (6.3% in our series); (2) “life-threatening hyperperfusion or malignant hyperperfusion” with marked increase (i.e., >100%) of PSV with CHS symptoms (2.0%); (3) “non-hyperperfusion damage or reperfusion damage” with no or little increase in PSV but with CHS symptoms and radiological changes (1.8%); and (4) “non-CHS patients” with no symptoms and no changes in TCD.

A limitation of this study is the time to perform the TCD post-CAS (i.e., 24 hours). If performed earlier it could have an impact on TCD data, although TCD was done in every CHS patient. Also, as mean flow velocity depends on both PSV and end-diastolic velocity value, it depends more on the image quality and the variability of different operators.

Therefore, we chose the most feasible measure (i.e., PSV) that is also widely accepted to decrease the possible variability between centers.

In conclusion, evidence of hyperperfusion >100% as a cut-off point for CHS diagnosis, seems to be not valid for routine clinical practice. Our proposal is to include evidence of hyperperfusion as major supportive CHS criteria but with no cut-off point for diagnosis, as missing diagnosis would prevent an early treatment of this severe complication.

**References**

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Figure 1. Comparison of peak systolic velocity (PSV) changes after carotid artery stenting (CAS) between the non-cerebral hyperperfusion syndrome (CHS) and CHS groups.
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