Supplementary Material 2. Transcranial Doppler grading of right-to-left shunt

Detection of even a single microembolic signal, also called a high intensity transient signal (HITS) during the test is considered a positive test for the presence of a right-to-left shunt (RLS). However, some neurosonologists do not consider the appearance of a solitary HITS as a positive test. The total number of HITS observed on the transcranial Doppler (TCD) during the entire recording represents the functional grading of RLS and is believed to represent the functional size of the shunt.

Currently, there are two grading systems to quantify (grading) RLS.

International Consensus criteria[1]:

Grade 0: no HIT
Grade 1: 1–10 HITS
Grade 2: 11–30 HITS
Grade 3: more than 30 HITS with "shower" or "curtain" appearance

Spencer's Logarithmic Scale[2]:

Grade 0: no HIT
Grade 1: 1–10 HITS
Grade 2: 11–30 HITS
Grade 3: 31–100 HITS
Grade 4: 101–300 HITS
Grade 5: more than 300 HITS

Various accuracy parameters for the two grading systems of RLS are shown in Supplementary Table 2.[3]

The so-called TCD bubble test detects only the presence of an RLS. The most common causes of a positive RLS study are PFO, atrial septal defect, and pulmonary arterio-venous fistula. However, there are no reliable and acceptable methods for differentiating between them.

Supplementary References

1. Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis* 2000;10:490-496.
2. Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* 2004;14:342-349.
3. Lao AY, Sharma VK, Tsivgoulis G, Frey JL, Malkoff MD, Navarro JC, et al. Detection of right-to-left shunts: comparison between the International Consensus and Spencer Logarithmic Scale criteria. *J Neuroimaging* 2008;18:402-406.

Supplementary Table 2. Diagnostic accuracy of International Consensus and Spencer Logarithmic Scale grading systems for RLS

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
International Consensus (any positive MES count)	100	72.4	32.1	100	64.1
Spencer Logarithmic Scale grade III+ (>30 MES)	100	91.3	60	100	85.5

RLS, right-to-left shunt; PPV, positive predictive value; NPV, negative predictive value; MES, micro-embolic signal.

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