

Comment 1.

This new indication is very interested and important for PFO closure for secondary stroke prevention. The caused factors of air embolic signal need to be described in more detail. The authors can provide more experience to ignore artefact in Figure 2 in technique as a tip for physician. And also show their successful rate for convincing the reader.

Thank you for your value comments. However, artefacts are mainly related with patients' co-operation. It is difficult to absolutely avoid artefacts. The multigated method may be useful for differentiation between embolic signals and artefacts. This technique samplings signals from different depths of the similar vessel to demonstrate the motion of the following embolus from proximal to distal. While an artifact shows no movement property but appears in all depths simultaneously ^[1].

1 Detection ICGoM, Bernd Ringelstein E, Droste DW, Babikian VL, Evans DH, Grosset DG, Kaps M, Markus HS, Russell D, Siebler M. Consensus on Microembolus Detection by TCD. *Stroke* 1998; **29**(3): 725-729 [DOI: 10.1161/01.Str.29.3.725]

2 Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. *New England Journal of Medicine* 2017; **377**(11): 1022-1032 [PMID: 28902590 DOI: 10.1056/NEJMoa1610057]

3 Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *New England Journal of Medicine* 2017; **377**(11): 1033-1042 [PMID: 28902580 DOI: 10.1056/NEJMoa1707404]

4 Mas J-L, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour J-C, Zuber M, Favrole P, Pinel J-F, Apoil M, Reiner P, Lefebvre C, Guérin P, Piot C, Rossi R, Dubois-Randé J-L, Eicher J-C, Meneveau N, Lusson J-R, Bertrand B, Schleich J-M, Godart F, Thambo J-B, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard J-M, Chatellier G. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. *New England Journal of Medicine* 2017; **377**(11): 1011-1021 [PMID: 28902593 DOI: 10.1056/NEJMoa1705915]

Comment 2.

Dear Editor, I read this manuscript and I think that the paper is good and well written.

Thank you!

Comment 3.

- Improve manuscript - include a discussion in order to compare the study with similar ones

Thank you for your comments. The comparisons of 3 major RCTs were added.

The recent three large randomized control trials (RESPECT, REDUCE and CLOSURE) demonstrated the benefit of PFO closure for secondary stroke prevention in selected cases of

patients with cryptogenic stroke [2-4]. RESPECT study was the longest follow-up of 6 years [2]. REDUCE study showed the benefit of PFO closure as compared with antiplatelet therapy at 3 years after treatment [3]. CLOSURE study included high embolic risk PFO with atrial septal aneurysm or large interatrial shunt [4]. Device-related atrial fibrillation was reported in REDUCE and CLOSURE [3,4].

Comment 4.

Please reference TOAST classification.

The reference was added.

Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24**(1): 35-41 [PMID: 7678184]

Please reference the following quantitative statements, "Prevalence of PFO is considerable as high as 25% of population. Moreover, around 50% of patients with cryptogenic stroke age less than 55 has PFO."

The reference was added.

Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, Coste J, Mas JL. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. *Stroke* 2002; **33**(3): 706-711 [PMID: 11872892]

When the authors state "The consideration of PFO as etiology of consecutive cryptogenic stroke became controversial since early clinical trials of PFO closure did not show any benefit for prevention of recurrent stroke [4]." they cite it with a case vignette article. Please actually cite the CLOSURE, RESPECT and PC trials.

The reference was added.

Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013; **368**(12): 1092-1100 [PMID: 23514286 DOI: 10.1056/NEJMoa1301440]

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012; **366**(11): 991-999 [PMID: 22417252 DOI: 10.1056/NEJMoa1009639]

Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Juni P. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013; **368**(12): 1083-1091 [PMID: 23514285 DOI: 10.1056/NEJMoa1211716]

The figure legends should be expanded to list the technique and the instrument make and model from which the reading was obtained.

The model of TCD machine was added to the figure legends.