Reviewer 1

The pathway of PFO is through coagulation pathway.

The treatment of ischemic stroke related PFO used anticoagulant agent and PFO closure.

The author explained thrombosis pathway rather than embolus pathway being out of common knowledge. (Management of Patients with Patent Foramen Ovale and Cryptogenic Stroke: An Update 2019.)

Authors: Thank you again for the careful reading of our manuscript and current revision.

We absolutely agree that patent foramen ovale (PFO) attributed ischemic strokes are of embolic origin. However, clot origin in PFO attributable stroke has not been resolved this far. The association of a PFO and ischemic strokes was so far based on epidemiologic studies mostly. Beside a venous to arterial (paradoxical embolic) pathomechanism, an in situ cardiac thrombosis has alternatively been considered as clot origin (Windecker, Stortecky et al. 2014). This is discussed in our manuscript in l. 41 and l. 153 ff. Here, we realized a misspelling in line l.153f., which may result in a misinterpretation of our depicted results, which we changed accordingly:

"Instead of a paradoxical embolic (venous to arterial) embolic source in PFO positive patients, an in situ intracardial thrombosis may be alternatively considered as clot origin."

Though exploratory, this is the first study suggesting a pathophysiologic impact of a PFO on cryptogenic ischemic stroke occurrence with a possible venous to arterial (paradoxical embolic) embolic source based on histological findings. In our opinion, the impact of the coagulation pathway on PFO attributable strokes is currently not finally resolved, neither by literature nor by our data. As we assume a paradoxical embolic source based on the depicted histological findings, we agree with your remark that the coagulation pathway may be of relevance and ought to be addressed in future trials. Therefore, we adapted the manuscript following your suggestions during the first revision (l. 199 ff.).

„Additionally, the impact of prothrombotic parameters on histological thrombus composition is currently unclear and may present a possible confounder, which ought to be addressed by future prospective trials. The addition of immunohistochemical staining methods to selectively address minor thrombus components and prothrombotic factors seem relevant in future histological clot classification."

Being derived by mechanical thrombectomy, we termed the analyzed histological clots "thrombi". This term has been commonly used in the presented literature (Simons, Mitchell et al. 2015, Bacigaluppi,

Semerano et al. 2019, Fitzgerald, Mereuta et al. 2019, Alkarithi, Duval et al. 2021). However, and as discussed above, this may lead to an obvious misunderstanding by the lack of a correct differentiation between an embolus and a thrombus. Following your remark, we revised our manuscript carefully to clarify our statement and applied to established term “cerebral clot” to avoid this misunderstanding. The applied changes are marked in the manuscript.

Thank you again for these helpful comments.

References

Alkarithi, G., et al. (2021). "Thrombus Structural Composition in Cardiovascular Disease." Arteriosclerosis, Thrombosis, and Vascular Biology **41**(9): 2370-2383.

Bacigaluppi, M., et al. (2019). "Insights from thrombi retrieved in stroke due to large vessel occlusion." Journal of Cerebral Blood Flow & Metabolism **39**(8): 1433-1451.

Fitzgerald, S., et al. (2019). "Correlation of imaging and histopathology of thrombi in acute ischemic stroke with etiology and outcome." J Neurosurg Sci **63**(3): 292-300.

Simons, N., et al. (2015). "Thrombus composition in acute ischemic stroke: a histopathological study of thrombus extracted by endovascular retrieval." J Neuroradiol **42**(2): 86-92

Windecker, S., et al. (2014). "Paradoxical embolism." J Am Coll Cardiol **64**(4): 403-415.