the same emanates from the comprehension of the fact that an ongoing inflammatory process leads to pulmonary arterial hypertension (aggravated by hypoxia, positive pressure ventilation and stiff-lung syndrome associated with COVID-19) culminating as accentuated right atrium (RA) pressures augmenting paradoxical embolization from the RA to left atrium (LA) through the PPFO (precluded in healthy subjects owing to the positive physiological LA-RA pressure gradient).[7,8]

The aforementioned constitutes a cardiac anaesthesiologists' perspective on opening yet another Pandora's Box (referring to a PPFO in this case) concerning the mechanisms leading to stroke in COVID-19 (which in itself has evolved to be nothing less than a natures' misadventurous stroke) highlighting the significance of a routine echocardiographic surveillance in this predisposed critically ill cohort.

Authors' contribution

RM conceptualized and wrote the entire manuscript.

Conflicts of interest

We do not have any conflict of interest, any commercial or financial interest in this material & agree to abide by the rules of your journal regarding publication of this article.

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Reply☆

Réplica

Dear Editor:

We are grateful to the author of the letter to the editor ''COVID-19 related strokes: Pandora's box may open as the p(c)lot thickens!'' for his interest in our article.[1] In the early months of the COVID-19 pandemic, it was suggested that the prothrombotic state observed in patients with the disease may be an aetiopathogenic mechanism of ischaemic stroke.[1,2] A year later, this hypothesis seems plausible, given the high frequency of thrombotic events reported in patients with severe COVID-19,[3,4] including ischaemic stroke, with an incidence of 1%-1.7% according to different series.[5,6] The exact mechanism triggering this prothrombotic state is currently unknown, although the process is probably multifactorial, conditioned by the systemic inflammatory response, increased concentration of angiotensin II in the blood, and direct endothelial invasion by the SARS-CoV-2 virus, as well as other pre-existing prothrombotic risk factors.[7,8]

However, we agree with the author of the letter that the prothrombotic state may not be the only factor involved in stroke in patients with COVID-19, given that ''ischaemic stroke may be caused by multiple, complex pathogenic mechanisms, particularly in patients with respiratory involvement.''[1] In accordance with the above, the letter to the editor suggests that patent foramen ovale (PFO) may cause ischaemic stroke due to paradoxical embolism, conditioned by a pressure gradient from the right to the left atrium secondary to pulmonary hypertension in patients with COVID-19. This theory seems plausible from a pathophysiological viewpoint, as PFO is present in up to 27% of the general population and more than 40% of patients with embolic stroke of undetermined source.[9] Furthermore, the persistent cough in these patients, a Valsalva manoeuvre, may increase the right atrial pressure gradient caused by pulmonary hypertension, favouring opening of the PFO.[9] A recent meta-analysis estimates the prevalence of stroke in patients with pulmonary hypertension at 8%.[10] Nonetheless,

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this association is controversial due to limitations of the studies reviewed, with some not treating stroke as the primary endpoint or not reporting stroke aetiology.[10]

We also concur that aetiological study is essential in cases of stroke, and that ruling out the presence of PFO may be important from an aetiopathological viewpoint. When PFO is detected, we must first consider whether or not it is related to stroke; the Risk of Paradoxical Embolism (RoPE) score may be used for this purpose. Secondly, we must assess whether PFO closure is indicated, taking into account such factors as age, magnitude of the shunt, and/or presence of atrial septal aneurysm.[11] However, in patients with COVID-19, who often present comorbidities and who may present severe acute respiratory failure, we must consider the risk-benefit balance of an intervention that is not free of potential complications.[9] Therefore, we agree on the need for aetiological study of ischaemic stroke in patients with COVID-19 and that PFO may be a causal factor. However, this association must be analysed in prospective studies, and identifying PFO in these patients is unlikely to influence acute management in most cases.

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Reply

Réplica

COVID-19 related strokes

Dear Editor:

In the letter to editor with title ''COVID related strokes: Pandora's Box may open as the p(c)lot thickens'', to the COVID-19-specific stroke etiologies that have been hypothesized (prothrombotic state, cardiomyopathy, endothelial damage, sepsis with hypothension), another one is added: pulmonary hypertension that would cause or increase a right-to-left shunt through an until then incidental patent formamen ovale (PFO). Chronic pulmonary hypertension increases the risk of stroke[1] but COVID-19-associated pulmonary hypertension is usually transient and there is debate about an increased risk of stroke with larger PFO or bigger right-to-left shunts.[2,3] Additionally to paradoxical embolism, pulmonary hypertension is associated to atrial fibrilation and polycithemia, which need different treatments to reduce their stroke risk. We have yet few data about the increase in stroke risk that the proposed mechanism — or other related to COVID 19 — will add. Until it is clarified we should be vigilant and include an echocardiogram in the study of COVID-19-related strokes, not only due to PFO and pulmonary hypertension but to COVID-19-associated cardiomiopathy.[4]

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