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Search for Coagulopathy Does Not Obviate Search for Venous Thrombosis in Suspected Paradoxical Embolism

To the Editor:

Paradoxical embolism via a patent foramen ovale (PFO) has been suggested as a mechanism of otherwise unexplained, cryptogenic stroke.¹ Paradoxical embolism, however, can be diagnosed only if there is evidence of a venous thrombosis coexisting with arterial embolism and right-to-left shunting via a PFO. When looking for venous thrombosis in suspected paradoxical embolism, the diagnostic yield depends on the interval between the event and the investigation and the used diagnostic methods.² Diagnosing venous thrombosis in patients with suspected paradoxical embolism is sometimes difficult since the thrombosis (1) may be confined to the calf veins and thus only detectable by venography; (2) may be localized in places other than in the leg veins and thus not detectable by leg venography; (3) may be not the cause but the consequence of arterial embolism; or (4) may spontaneously dissolve, re-embolize, or recanalize.³ Due to these problems, a timely search for venous thrombosis is only rarely performed in patients with suspected paradoxical embolism, especially if they have no clinical symptoms of thrombosis. Several strategies are possible to overcome these obstacles. The first strategy is by improving noninvasive methods to visualize venous thrombosis in different locations, like magnetic resonance venography.⁴ Another strategy is by search for a clotting diathesis in patients with suspected paradoxical embolism. This indirect strategy is based on the assumption that hypercoagulability leads to a higher incidence of venous thrombosis and thus, in the presence of a PFO, might increase the possibility of paradoxical embolism. Hypercoagulability can be assessed by genetic testing for factor V_{G1691A} mutation, prothrombin_{G20210A} variant, and *TT677* genotype of methylenetetrahydrofolate reductase. The risk for venous thrombosis is increased 3- to 8-fold in heterozygous carriers of the factor V_{G1691A} mutation, 3-fold in heterozygous carriers of the prothrombin_{G20210A} variant, and only 0.16-fold in homozygous carriers of the *TT677* genotype of methylenetetrahydrofolate reductase.^{5,6}

Addressing the issue of understanding the pathophysiology of PFO-related strokes, the study of Pezzini et al looked for the prevalences of factor V_{G1691A} mutation, prothrombin_{G20210A} variant, and *TT677* genotype of methylenetetrahydrofolate reductase in patients with ischemic strokes occurring at >45 years of age.⁷ In patients with PFO-related strokes they found a higher prevalence of the prothrombin_{G20210A} variant and, to a lesser extent, factor V_{G1691A} mutation than in the remaining patients and in the controls after adjusting for age, sex, smoking, hypertension, and hypercholesterolemia. They conclude that these thrombophilic mutations may represent risk factors for PFO-related strokes. Although their findings are interesting and plausible, several issues have to be raised:

1. The creation of the PFO+ and PFO- group seems arbitrary, since 6 patients with PFO were included in the PFO- group. In these patients, priority was given to the other mechanism of stroke. Since several potential stroke mechanisms may coexist in an individual patient, why were the authors sure that it was not due to paradoxical embolism in these patients? If these 6 patients had been included in the PFO+ group, how would the results have changed?

2. The onset of stroke in close temporal relationship with a Valsalva maneuver renders paradoxical embolism into a more probable cause of stroke.² How many of the patients had a Valsalva maneuver in their history? Did this event influence the decision to include them in the PFO+ group?

3. Transthoracic and/or transesophageal echocardiography had been performed in all included patients. Did the authors also look for PFO by echocardiography and, if yes, were there any false-positive or false-negative cases when compared with transcranial Doppler?

4. Coagulation testing (prothrombin, activated partial thromboplastin times, antiphospholipid antibodies, fibrinogen, protein C, protein S, activated protein C resistance, and antithrombin) had been performed in all included patients. How were the relations between

coagulation test abnormalities and thrombophilic mutations in the PFO+ and PFO- groups?

5. In how many patients were investigations of the lower limbs performed and how were the results related with the prevalence of thrombophilic mutations in the PFO+ and PFO- groups?

6. Three of the patients in the PFO+ group had deep-vein thrombosis at the time of stroke. Did these 3 patients have thrombophilic mutations?

7. Risk factors for vascular events such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia were assessed. These are well-known risk factors for arterial atherosclerosis. Risk factors for the development of venous thrombosis, however, comprise previous thrombosis/pulmonary embolism, immobilization, previous surgery, malignancy, oral contraceptives, and hormonal replacement therapy. It has been shown that the clinical penetrance of the thrombotic tendency associated with the prothrombin_{G20210A} variant is more expressed in the presence of circumstantial risk factors.⁶ How was the prevalence of these risk factors in the different groups?

8. Is there any other explanation, besides paradoxical embolism, for the higher prevalence of thrombophilic mutations in the PFO+ than in the PFO- group?

In summary, the presented data are not convincing enough to recommend laboratory testing for coagulopathies in patients with PFO-related strokes. Neither will this way of testing clarify the question of whether the stroke is due to paradoxical embolism in a patient with PFO. Screening for mutations does not obviate the search for venous thrombosis when looking for paradoxical embolism. In contrast with the authors, we do not believe that "deep-vein thrombosis in stroke patients with PFO is usually undetectable." If paradoxical embolism really exists, venous thrombosis has to be diagnosed at the right time by using the appropriate diagnostic methods.

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Response

We appreciate Drs Stöllberger and Finsterer's critical comments on our article concerning the role of inherited thrombophilic disorders in PFO-related cerebral infarcts.

Venous thrombosis may remain undetected in many cryptogenic strokes because of its location, the size of the thrombus, the timing of investigation, and the use of inappropriate diagnostic methods, leading to a probable underestimation of paradoxical embolism. Therefore, we do not dispute the fact that an unbiased search for a venous source of emboli should be carried out in all patients with PFO and ischemic stroke of otherwise unexplained origin. However, the assumption that paradoxical embolism could be indirectly suspected when PFO and a clotting diathesis are coexistent in patients without any definitive cause of stroke should be interpreted with caution. The fact that the risk of venous thrombosis is increased in subjects with inherited thrombophilic disorders does not necessarily implicate that the mechanism of stroke is paradoxical embolism in all these cases. As we point out in our article, alternative pathomechanisms linking PFO and cerebral ischemia might be operant and cannot be ignored.^{1,2} This is relevant when interpreting the results of the studies examining the role of hypercoagulable states in PFO-related stroke.

With regard to the specific issues, our comments are the following:

1. Of the 6 cases with PFO who were not included in the PFO+ group, 4 had had an angiographically proven spontaneous cervical artery dissection (sCAD). Although sparse reports suggest that the prevalence of PFO may be higher in patients with sCAD than in other subtypes of stroke,³ leading to the intriguing hypothesis of a common developmental defect, it seems unlikely that a cerebral ischemic event might be due to alternative causes in the presence of a recent sCAD. Thus, it is not reasonable to suspect paradoxical embolism in such cases. As to the remaining 2 cases, their inclusion in the PFO+ group would not have significantly changed the results of the study.

2. Six patients out of 36 (16.7%) in the PFO+ group had had a Valsalva maneuver or a Valsalva-like activity at stroke onset, compared with 9 out of 89 (10.1%) in the PFO- group. This difference was not statistically significant. As outlined in our article, the only inclusion criterion for the PFO+ group was the presence of a right-to-left shunt with no other definite cause of stroke (except for the prothrombotic genotypes under investigation).

3. A search for interatrial right-to-left shunt by contrast transesophageal echocardiography (TEE) was performed in 22 patients in the PFO+ group (61.1%) and in 30 patients in the PFO- group (33.7%). No evidence of interatrial shunt on TEE was found in 1 patient included in the PFO+ group. This discrepancy was attributed to the patient difficulty performing a complete Valsalva maneuver during TEE, because of sedation.⁴

As to the transthoracic echocardiography (TTE), its low diagnostic accuracy in the assessment of interatrial right-to-left shunt⁵ prevents any adequate comparisons with contrast-enhanced transcranial Doppler.

4. No significant difference between the PFO+ group and the PFO- group was observed with regard to the distribution of the other prothrombotic factors. In particular, 1 patient had low levels of protein C activity and 1 had low levels of protein S activity in the PFO- group versus 1 patient with protein S deficiency in the PFO+ group. Increased plasma levels of IgG anticardiolipin antibodies were found in 1 case in the PFO+ group.

5. Lower-extremity venous Doppler was performed in 34 patients (31 in the PFO+ group, 3 in the PFO- group). Three of them (all in the PFO+ group) had deep-vein thrombosis.

6. Thrombophilic mutations were found in 2 of the 3 patients with deep-vein thrombosis at the time of stroke (heterozygosity for the PT_{G20210A} variant and heterozygosity for the FV_{G1691A} mutation + PT_{G20210A} variant, respectively).

7. Circumstantial events predisposing to venous thrombosis were not systematically investigated in all subjects included in our series, except for the current use of oral contraceptives for women. Eighteen subjects out of 57 (31.6%) were users. Although a slightly higher frequency was observed in the PFO+ group than in the PFO- group (50.0% and 34.3%, respectively), this difference did not reach statistical significance.

8. As stated above, as well as repeatedly in our article, other mechanisms linking PFO to stroke, besides paradoxical embolism, have been presumed. The hypothesis that a systemic procoagulant state may increase the likelihood of all these pathophysiological processes is biologically plausible, although this remains to be established.

In summary, we believe Drs Stöllberger and Finsterer are incorrect in their interpretation of and conclusions about the results of our study, as our findings do not suggest or imply that coagulation testing may obviate the search for venous thrombosis in patients with PFO and cerebral ischemia. As to the appropriateness of coagulation testing in patients with PFO-related stroke, our observations have been recently confirmed by separate groups of investigators.^{6,7}

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