

Histological Composition and the Origin of the Thrombus A New Diagnostic Assay for Secondary Stroke Prevention?

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Between one third and one half of strokes will have no known cause following thorough diagnostic evaluation.¹ This complicates effective secondary stroke prevention. In fact, a recent stroke classification validation approach has shown that etiologic classification systems for stroke subtype have between 0.61 (poor) to 0.71 (fair) area under the receiver operating characteristic curve for stroke recurrence within 90 days.¹ In light of recent trials showing effective mechanical thrombectomy with complete or near complete removal of the embolus in most cases of emergent large vessel occlusion,²⁻⁵ an opportunity has arisen for sensitive and specific assays of the removed clot to determine stroke cause.

With expanding interest in the endovascular treatment of stroke, more research emphasis has been placed on the imaging, composition, and mechanical characteristics of the clots causing large vessel occlusions. Early work attempted to compare clot composition with imaging characteristics and examine correlations to treatment response (both intravenous thrombolysis and mechanical thrombectomy).⁶⁻⁹ Although we seek technology that will allow for efficient recanalization in all cases, it may well be that advanced imaging approaches, potentially noninvasive or intravascular, will be required to discern clot characteristics that then dictate the appropriate thrombectomy system or technique. Other applications of clot analysis include mechanical measurements of thromboemboli extracted from patients, which has informed the manufacture of clot analogs made on the bench to develop in the preclinical phase the next-generation medical devices for thrombectomy.¹⁰⁻¹³ Finally, improved pathological analysis of retrieved clot to serve as a diagnostic assay for stroke cause has been proposed. Traditionally, the standard pathology report of the extracted embolus reveals “clot.” Deploying more sophisticated histological techniques has supported that

CD3⁺ T-cell counts in the retrieved clots may be useful to identify strokes of atherothrombotic origin.¹⁴

A recent meta-analysis described that red blood cell-rich clots produce hyperdense artery sign on CT and are associated with improved recanalization rates; however, no association for stroke cause and histopathologic composition of thrombi could be ascertained.¹⁵ Importantly, this systematic review concludes that much work remains to be done to perform more sophisticated pathological analyses in an effort to ascertain associations with the cause of the stroke. To achieve these goals, a consensus statement from international experts sought to solidify terminology and establish fundamental analyses to advance the field.¹⁶ A multicenter study led by the Mayo Clinic (STRIP [Stroke Thromboembolism Registry of Imaging and Pathology]) seeks to couple clot histopathologic and imaging characterization with clinical data and procedural outcome measures.

In this issue, Sporns et al¹⁷ provide one of the largest studies to date interrogating the question of associations between clot characteristics and stroke subtype as defined by TOAST (Trial of ORG 10172 in Acute Stroke Treatment). A comprehensive histopathologic protocol was performed and also included immunohistochemical techniques to examine the extent of lymphocyte and macrophage activity in the thrombi. Among the key findings are that composition varied between emboli of cardiac and noncardiac origin. Namely, fibrin-rich thrombi had a significant correlation with cardiac source. Using the histological fingerprint from the first part of the study, they found that retrieved material from cryptogenic strokes was most likely to be from a cardiac source. This raises an important hypothesis that anticoagulation may be beneficial in cryptogenic stroke. These findings are supported by a recent study demonstrating atrial fibrillation to be underestimated in ischemic stroke.¹⁸ Atrial fibrillation was found in 14% of patients with acute ischemic stroke presenting with sinus rhythm when enhanced and prolonged rhythm monitoring was achieved as compared to 5% in patients with standard care. Overall, this large study by Sporns et al¹⁷ makes an important contribution to the field by showing the potential of clot histopathology to discern stroke cause and potentially guide secondary stroke prevention measures.

Emboli retrieved from stroke patients are complex, heterogeneous, and anisotropic materials that undergo a dynamic evolution. Compositional fingerprints may be age dependent altering the specificity and sensitivity for stroke cause determination. Moreover, diagnostic pathological evaluation will require consideration that thrombi causing a large vessel occlusion can change with time, for example, with clotting in situ because of flow stagnation at the borders of the original embolus. However, with mechanical thrombectomy now

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standard of care for emergent large vessel occlusions, there is clearly much to be learned from the extracted embolus.

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