Ischemic stroke of undetermined cause is a major health issue because of its high frequency and clinical relevance. Histopathologic analysis of human thrombi, retrieved from stroke patients with large-vessel occlusion during mechanical thrombectomy, may provide information about underlying pathologies. This study examines the relationship between stroke causes and histological clot composition to identify specific patterns that might help to distinguish causes of cryptogenic stroke. Thrombi of 145 consecutive stroke patients with large-vessel occlusion were collected during intracranial mechanical recanalization. The hematoxylin and eosin-stained specimens were quantitatively analyzed in terms of the relative fractions of the main constituents (red and white blood cells and fibrin/platelets). These data, along with additional clinical and interventional parameters, were compared for different stroke subtypes, as defined by the international Trial of Org 10172 in Acute Stroke Treatment criteria. The composition of thrombi from cardioembolic and noncardioembolic stroke patients differed significantly for all main thrombus components. Cardioembolic thrombi had higher proportions of fibrin/platelets ($P=0.009$), less erythrocytes ($P=0.003$), and more leucocytes ($P=0.035$) than noncardioembolic
thrombi. Cryptogenic strokes showed strong overlap with cardioembolic strokes but not with noncardioembolic strokes, in terms of both thrombus histology and interventional and clinical outcome parameters. Quantitative evaluation of thrombus composition may help to distinguish between different stroke causes. Our findings support the notion that the majority of cryptogenic strokes are cardioembolic.