Cardiac Thrombogenicity in Stroke: Mechanisms and Evaluation

At the European Society for Vascular Surgery 36th Annual Meeting, a session on Heart, stroke and the vascular surgeon addresses the importance of identifying cardiac thrombogenicity in the evaluation of ischemic stroke risk. The ischemic embolic stroke trio plays different instruments of thrombogenicity to compose the cardioembolic stroke from tones of cardiac, vascular and systemic origin (Fig 1). The systemic thrombogenicity has been long recognized through measures of coagulation and platelet aggregation. With the deciphering of atherothrombosis pathophysiology, specific local factors are emerging behind the ischemic stroke, with the systemic chords being accompanied by vascular thrombogenicity. To fully distinguish the parts of the ischemic stroke trio, the specific cardiac thrombogenicity needs to be recognized.

STRUCTURAL AND ELECTRICAL CARDIAC THROMBOCYGENITY

Structural cardiac affections, e.g. valvular heart disease, ventricular wall motion abnormalities and patent foramen ovale (PFO) are common sources of cardioembolic strokes. Foremost, confirmed or suspected atrial fibrillation (AF) is central for the cardiac thrombogenicity, with AF screening being a preventive approach. However, risk stratification by the CHA2DS2-VAsc score for targeting the thrombogenicity with anti-coagulation treatment for stroke prevention applies only when AF is detected. This reinforces the need for clinically useful biomarkers of cardiac thrombogenicity.

NATRIURETIC PEPTIDES IN CARDOEMBOLIC STROKE

Cardioembolic strokes exhibit increased levels of B-type natriuretic peptide (BNP) and its precursor N-terminal peptide (NT-proBNP). A meta-analysis of twenty-three studies reported an increased sensitivity and specificity for prediction of cardioembolic stroke when the BNPs were added to the model. The BNP release from cardiomyocytes reflects an increased cardiac wall stress, which may serve as a sensible sign of increased cardiac thrombogenicity. It should however be noted that the link of BNP to cardioembolic stroke origin may as well be as a marker of AF. The importance of atrial load as a predisposing marker for AF in cardioembolic stroke is supported by independent association of the mid-regional atrial natriuretic peptide precursor peptide (MRproANP) for cardioembolic stroke risk.

ATRIAL MYOPATHY BEHIND CARDIAC THROMBOGENICITY

Even if atrial and B-type natriuretic peptides may not rule out AF as an underlying cardioembolic cause, left atrial (LA) remodelling may appear long before the onset of AF. Furthermore, decreased LA reservoir and contraction function, which can be routinely measured by echocardiographic atrial strain analysis, are observed in cardioembolic strokes, even in the absence of AF on prolonged screening. These observations have raised the notion that LA remodelling and dysfunction as reflection of atrial myopathy - without presence of AF — represents a subclinical phase of increased cardiac thrombogenicity that may be susceptible for preventive interventions. Importantly, reduced left atrial strain may represent a modifiable risk factor, since improved atrial strain has been reported after a 1-2 year physical activity program in subjects with rheumatoid arthritis.

INFLAMMATORY BIOMARKERS ARE INCREASED IN CARDIAC AND VASCULAR THROMBOGENICITY

Inflammatory biomarkers are increased in embolic compared with other ischemic strokes causes. However, inflammation is a hallmark of atherosclerosis being driven by a lack of functional resolution of inflammation in the vascular wall. A meta-analysis summarizing fourteen studies of C-reactive protein (CRP), five studies of tumour necrosis factor (TNF) α, and four studies of interleukin (IL) 6 confirmed no significant differences for these inflammatory biomarkers in embolic stroke of either cardiac or vascular source. These findings illustrate the connection of atherothrombotic embolic stroke with inflammation through the chronic inflammation in large artery atherosclerosis (LAA), and also point to cardiac thrombogenicity being inflammatory to a similar extent. The unspecific characteristic inflammation however limits the use of these biomarkers in current risk assessment of cardioembolic stroke. Further work may help to establish a potential value of markers of inflammation in cardiac thrombogenicity.

IMMUNOTHROMBOSIS: A KEY FEATURE OF CARDIAC THROMBOGENICITY

Cardioembolic clots retrieved during cerebral thrombectomy are highly inflammatory. In addition to higher leukocyte proportion compared with other origins, cardiac emboli are particularly rich in neutrophil extracellular traps (NETs). In a direct comparison, NET stainings are significantly higher in cardioembolic compared with atherothrombotic cerebral clots. These findings raise the notion of immunothrombosis, characterized by leukocyte-platelet aggregates, prevailing particularly in cardiac thrombogenicity. The findings of NET
enrichment in cardiac emboli implies a dominating neutrophil immunothrombosis in cardiac thrombogenicity. Although analyses of thrombectomies are difficult to perform in practice, it is important to note that also systemic measures of NET proxies, namely cell free DNA (cfDNA) and citrullinated histones (citG3), are higher in cardioembolic compared to atherothrombotic stroke.11

A DOUBLE HIT CARDIAC THROMBOGENICITY — LESSONS FROM THE COVID-19 PANDEMIC

Increased neutrophil immunothrombosis is observed in corona virus diseases 2019 (COVID-19),12 which has been associated with increased ischemic stroke incidence.13 This provides further circumstantial evidence reinforcing the importance of the neutrophil immune thrombogenicity for cardioembolic stroke. Taken together, the possibility of a double-hit phenomenon should be considered where systemic factors add to and further drive local cardiac mechanisms. For example, a systemically activated immunothrombosis may boost the consequences of an atrial myopathy. Hence, two separate subclinical thrombogenic phases may converge into cumulated cardiac thrombogenicity and increased cardioembolic stroke risk.

SUMMARY

Thrombogenicity behind embolic stroke should be considered both from a systemic and local (myocardial or vascular) point of view. The local processes in the vascular wall leading to atherothrombosis are in part shared with cardiac thrombogenicity, for example through inflammation, but also reveal distinct immunothrombosis features. The mechanic cardiac thrombogenicity reflected by e.g. natriuretic peptides and echocardiographic LA remodelling and strain exhibit the potential to be incorporated with circulating biomarkers and clinical findings in the evaluation of cardioembolic stroke risk.

In conclusion, robust markers of cardiac thrombogenicity beyond the observation of overt AF, may become instrumental to refine the stroke risk stratification and to define cardiac thrombogenicity for advanced anticoagulant stroke prevention strategies.

DISCLOSURE

The author reports no conflicts of interest related to this work.

REFERENCES

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