Editorial

Left atrial appendage closure: shutting down the coagulation factory hall

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The left atrial appendage (LAA) is considered to be the major site for clot formation in patients suffering from atrial fibrillation (AF). Thrombi originating from the LAA may migrate to the systemic circulation and block peripheral arteries, and occlusion of cerebral arteries is especially notorious due to the impact of ischemic stroke. Several LAA properties have been related to increased thromboembolic risk, such as non-chicken wing morphology (1), lower LAA flow velocity (2), and possibly local thrombotic milieu as determined by hemostatic biomarkers (3).

Over the past decades, the LAA has developed to become an important mechanical target for thromboembolic risk reduction, thereby expanding the methods for exclusion of the LAA from the circulation. Current methods include placement of endocardial devices (such as Watchman FLX and Amplatzer Amulet), epicardial devices or clips (such as Lariat and AtriClip) or surgical amputation. However, while a variety of approaches emerges, their influence on local and systemic hemostasis remains largely unclear for now.

In this issue of JTD, Litwinowicz *et al.* (4) investigate coagulation and fibrinolysis in atrial fibrillation patients with high thromboembolic risk undergoing stand-alone epicardial LAA exclusion by Lariat (73%) and AtriClip (27%). By performing fibrin clot analysis in peripheral blood, the authors demonstrate decreased fibrin clot permeability and increased clot lysis time at discharge compared to baseline, indicating a period of increased thrombogenicity following intervention. Interestingly, a similar pattern of initial coagulation activation can be observed after endocardial LAA closure, with pro-coagulant parameters increasing in the initial period after closure, and returning to baseline levels after about one month (5). These biomarkers play significant roles in hemostasis and fibrinolysis and their increase may indicate a temporal prothrombotic state.

This may add to the baseline prothrombotic state that is present in patients with AF as demonstrated by elevated levels of various hemostatic biomarkers (6). AF leads to atrial fibrosis and inflammatory processes and is associated with increased VWF and PAI-1 levels, possibly resulting from endothelial activation (7). Moreover, absence of atrial contractions due to AF causes low flow conditions, especially in the generally small and elongated, trabeculated structure that is the LAA. In combination with diminished local blood flow and endothelial activation, a prothrombotic or hypercoagulable state is one of the three pillars that can induce clot formation as described by Virchow's triad. All three pillars are present in AF patients, contributing to the baseline prothrombotic state.

Interestingly, the authors show that hypercoagulability is more prominently present in the LAA than in peripheral blood, confirming results from their earlier publication (8). This underlines the hypothesis that the LAA is the coagulation factory hall that keeps polluting the blood and makes AF patients susceptible to clot formation. On the other hand, AF may be the manifestation of a multifactorial systemic

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disease. Especially in patients with high CHA_2DS_2-VASc scores, and thus multiple comorbidities, thrombus formation can be induced by other mechanisms than those only locally present in the LAA, including hypertension, atherosclerosis, and diabetes mellitus (9). This makes it difficult to gauge how local and systemic prothrombotic milieu influence each other and raises the question in whom LAA closure yields the highest clinical benefit; those with higher or lower thromboembolic risk.

Taking the baseline presence of a prothrombotic state in AF patients into account, it is promising to see that one month after epicardial LAA closure, patients show increased clot permeability and shortened clot lysis time compared to baseline. Clot properties improve after closure, which implicates a more favorable thrombotic profile. Moreover, as blood was taken peripherally, this suggests that closing off the LAA from the circulation results in a reduction of not only local, but also peripheral thrombogenicity. This suggests that shutting down the coagulation factory hall freshens the blood down the stream.

In the current study, all patients were switched from OAC to aspirin monotherapy after closure, while being bridged with low-molecular weight heparin during hospital stay. Fibrin clot permeability, clot lysis time, and especially endogenous thrombin potential (ETP) may improve under oral anticoagulation therapy (OAC). Aspirin is however not expected to influence these markers and may not be the optimal antithrombotic regimen in the first period following occlusion due to increased thrombogenicity. It is questionable if similar results would have been obtained in patients on OAC after closure, as ETP would be suppressed. When directly using ETP as a surrogate for thrombotic risk, one might even state that OAC may be the therapy of choice in patients without very high bleeding risk. The LAAOS III trial (10) showed a 33% reduction in a composite endpoint of ischemic events in patients receiving concomitant LAA exclusion when undergoing cardiac surgery. Half of the patients in this trial underwent LAA amputation, whereas the other half of LAAs was closed by staple, clip, or from within. Importantly, patients remained on OAC therapy after closure and it is unclear if similar results would have been achieved in patients receiving antiplatelet therapy.

The studied biomarkers may have a role as a predictor of events or in risk stratification. The use of ETP and thrombin generation assays for predicting thrombotic events has been described (11), but is nonetheless not yet well established—partly due to the absence of standardized methods. Novel methods involve the use of whole blood instead of platelet-poor plasma, potentially better reflecting *in vivo* hemostasis (12). Likewise, it would be interesting to evaluate whether hemostatic or fibrinolytic biomarkers are associated with post-procedural leaks, but none were detected in the current study. This may simply be a result of the limited sample size, as leaks are not uncommon following Lariat LAA exclusion. Moreover, transthoracic echocardiography was used during follow-up imaging, while this is not the preferred modality to diagnose these leaks (13). Notably, presence of a post-procedural leak has been associated with the occurrence of thromboembolic events following epicardial LAA exclusion (14).

This paper aids in unravelling the mechanisms involved in thrombus formation in AF patients. Furthermore, it underlines the importance of the LAA in coagulation activation and the beneficial effect of LAA exclusion on fibrinolysis, endorsing the systemic effects of "dismantling the prothrombotic factory" by exclusion of the LAA from the circulation. Future studies should further investigate the interplay between local and systemic hemostatic milieu. Additionally, subgroup analyses investigating the benefit of LAA exclusion in patients with high and low CHA_2DS_2-VASc score are warranted.

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