



## Editorial

## Connecting atrial morphology with platelet reactivity: What the left atrial appendage can tell us about the procoagulant state in atrial fibrillation



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Atrial fibrillation (AF) remains the most common form of heart rhythm disorder and a leading cause for stroke and mortality. A major challenge for comprehensive AF prevention and management is the timely identification and risk stratification of patients requiring treatment.

AF is considered as associated with a pro-coagulant state, characterized by augmented platelet activation and predisposition to intra-atrial thrombi and stroke. In turn, hypercoagulability *per se* appears to support AF development and progression, largely attributable to pleiotropic actions of coagulation factors through cellular protease-activated receptors, or PAR [1]. Although our understanding of the bidirectional association of AF and stroke is growing, the respective roles of rhythm dysfunction and abnormalities of the atrial and/or systemic substrate remain blurred. An open question is how precisely do changes in atrial rate translate into altered thromboembolic propensity? It is known that cardiomyocytes themselves can trigger and propagate inflammatory signaling, particularly during AF, through NLRP3 inflammasome activation. This positions the cardiomyocyte NLRP3 inflammasome and its major product (IL)-1 $\beta$  as potential links between AF and thromboembolism [2,3]. Indeed IL-1 $\beta$  can drive platelet hyper-activation and spreading, leading to pro-coagulant viscoelastic properties of the blood [4]. Thus platelets might be considered as inflammatory cytokine sensors and health indicators, but it is still not clear to what extent changes in platelet function directly reflect the degree of atrial inflammation.

The report by Kosiuk et al. published in this issue of the *International Journal of Cardiology* [5], extends our understanding of the association between platelet changes and atrial remodeling in AF (insert citation). The authors examined the characteristics of left atria (LA) and LA appendages of patients with paroxysmal or persistent AF, correlating them with baseline platelet activity and the residual responsiveness to thrombin receptor activation. The major finding of the study was that

increased LAA volume was significantly associated with a pro-coagulant state in AF, while neither LAA or LA morphology, nor LA function, correlated with enhanced pre-activation of platelets. This finding is consistent with an earlier report showing an association of LAA volume, but not atrial dysfunction, with cardioembolic stroke in AF [6]. In the present study [5], pre-activated platelets were subsequently less responsive to thrombin receptor activation *ex vivo*, indicating receptor consumption. While the authors did not confirm desensitization with specific antibodies against the uncleaved (non-activated) and cleaved (activated) forms of the major thrombin receptor PAR1, the observations fit with previous reports showing reduced *ex vivo* platelet reactivity to thrombin receptor activation in AF [7]. Intriguingly, the direct thrombin inhibitor dabigatran apparently resensitizes thrombin receptor reactivity in AF patients, by increasing PAR1 and PAR4 density on the platelet surface [8]. This resensitization is evident within 12 h after first intake of dabigatran, likely reflecting translational effects and/or shuttling from intracellular pools or previously internalized receptors, and is specific for thrombin-activated receptors. Whether the direct factor X inhibitors (“xabans”) also modify platelet PAR density and hence reactivity needs direct demonstration. In the present study, 7% of patients were on dabigatran, the overwhelming majority (one-third) of all subjects received a xaban [5]. The possibility that oral coagulant therapy itself modifies platelet reactivity, thereby blurring the consequences resulting from the increased LAA volume, needs to be addressed in subsequent studies.

A puzzling finding was the apparent lack of association between changes in LA or LAA characteristics, and circulating microparticles (MP). In the present study, only those patients with concomitant diabetes showed elevated platelet MP levels. Platelet MP, particularly phosphatidylserine-exposing MP, have emerged as candidate mediators of the pro-coagulant state in AF [9] and endothelial-derived MP predict AF recurrence, along with hsCRP, implicating inflammatory processes as a potential trigger of AF. Since MP-bound IL-1 $\beta$  predicts platelet pre-activation [10], it is possible that atrial NLRP3 inflammasome-derived IL-1 $\beta$  may contribute the pro-coagulant state in AF. Future studies assessing the precise role of circulating MP as potential biomarkers of a low-grade chronic inflammatory state in the heart, particularly the atria, might help establish and validate the potential link between inflammation, thromboembolism and AF.

In an ideal world, the cardiologist can quickly and reliably identify and quantify the patient's risk of stroke and progression of AF. Platelets are readily accessible and techniques for functional evaluation are routinely available. However, before the platelet can provide a window to what is going on in the atria, additional studies such as the one

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highlighted [5] here will be required. Importantly, observations made in blood *ex vivo* must be thoroughly validated against the alterations in the atrial tissue, and standardized protocols established.

#### Declarations of interest

None.

#### References

- [1] H.M. Spronk, A.M. De Jong, S. Verheule, H.C. De Boer, A.H. Maass, D.H. Lau, M. Rienstra, A. van Hunnik, M. Kuiper, S. Lumeij, S. Zeemering, D. Linz, P.W. Kamphuisen, H. Ten Cate, H.J. Crijns, I.C. Van Gelder, A.J. van Zonneveld, U. Schotten, Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation, *Eur. Heart J.* 38 (2017) 38–50, <https://doi.org/10.1093/eurheartj/ehw119>.
- [2] L. Scott Jr., N. Li, D. Dobrev, Role of inflammatory signaling in atrial fibrillation, *Int. J. Cardiol.* (2018) <https://doi.org/10.1016/j.ijcard.2018.10.020>.
- [3] C. Yao, T. Veleva, L. Scott Jr., S. Cao, L. Li, G. Chen, P. Jeyabal, X. Pan, K.M. Alsina, I. Abu-Taha, S. Ghezelbash, C.L. Reynolds, Y.H. Shen, S.A. LeMaire, W. Schmitz, F.U. Muller, A. El-Armouche, N.T. Eissa, C. Beeton, S. Nattel, X.H.T. Wehrens, D. Dobrev, N. Li, Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation, *Circulation* (2018) <https://doi.org/10.1161/CIRCULATIONAHA.118.035202>.
- [4] J. Bester, E. Pretorius, Effects of IL-1beta, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity, *Sci. Rep.* 6 (2016) 32188, <https://doi.org/10.1038/srep32188>.
- [5] J. Kosiuk, T. Uhe, C. Stegmann, L. Ueberham, L. Bertagnolli, N. Dargès, B. Dinov, A. Müssigbrodt, S. Richter, I. Paetsch, C. Jahnke, Morphological determinators of platelet activation status in patients with atrial fibrillation, *Int. J. Cardiol.* (2018) <https://doi.org/10.1016/j.ijcard.2018.11.096>.
- [6] W.K. Jeong, J.H. Choi, J.P. Son, S. Lee, M.J. Lee, Y.H. Choe, O.Y. Bang, Volume and morphology of left atrial appendage as determinants of stroke subtype in patients with atrial fibrillation, *Heart Rhythm.* 13 (2016) 820–827, <https://doi.org/10.1016/j.hrthm.2015.12.026>.
- [7] L. Pourtau, J.M. Sellal, R. Lacroix, P. Poncelet, O. Bernus, G. Clofent-Sanchez, M. Hocini, M. Haissaguerre, F. Dignat-George, F. Sacher, P. Nurden, Platelet function and microparticle levels in atrial fibrillation: changes during the acute episode, *Int. J. Cardiol.* 243 (2017) 216–222, <https://doi.org/10.1016/j.ijcard.2017.03.068>.
- [8] A. Achilles, A. Mohring, L. Dannenberg, M. Grandoch, T. Hohlfeld, J.W. Fischer, B. Levkau, M. Kelm, T. Zeus, A. Polzin, Dabigatran enhances platelet reactivity and platelet thrombin receptor expression in patients with atrial fibrillation, *J. Thromb. Haemost.* 15 (2017) 473–476, <https://doi.org/10.1111/jth.13595>.
- [9] L. Wang, Y. Bi, M. Yu, T. Li, D. Tong, X. Yang, C. Zhang, L. Guo, C. Wang, Y. Kou, Z. Dong, V.A. Novakovic, Y. Tian, J. Kou, M.A. Shammam, J. Shi, Phosphatidylserine-exposing blood cells and microparticles induce procoagulant activity in non-valvular atrial fibrillation, *Int. J. Cardiol.* 258 (2018) 138–143, <https://doi.org/10.1016/j.ijcard.2018.01.116>.
- [10] S. Ederhy, E. Di Angelantonio, Z. Mallat, B. Hugel, S. Janower, C. Meuleman, F. Boccara, J.M. Freyssinet, A. Tedgui, A. Cohen, Levels of circulating procoagulant microparticles in nonvalvular atrial fibrillation, *Am. J. Cardiol.* 100 (2007) 989–994, <https://doi.org/10.1016/j.amjcard.2007.04.040>.