Platelet Activation after Radiofrequency Ablation in Atrial Fibrillation:

Is There Any Clinical Implication?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population and in patients undergoing cardiac surgery. AF is a self-perpetuating arrhythmia which is facilitated by structural and functional changes elicited by atrial high rate activity. Shortening of atrial effective refractory period is the earliest functional change that characterizes atrial remodeling. As prevalence of AF increases with advancing age, its social impact is becoming very relevant because of the associated high risk of cardiovascular events and increased morbidity and mortality. AF is complicated by stroke of thrombo-embolic origin, which is thought to stem from thrombus formation, generated in the left atrial appendage with ensuing embolism in the cerebral circulation. However, AF patients may also suffer from cardiovascular events which occur as a consequence of the atherosclerotic disease. Thus, AF is typically associated with different risk factors of athero-thrombosis including hypertension, diabetes and dyslipidemia and with systemic signs of atherosclerosis. This has been documented in the thoracic aorta and, more recently, in the peripheral circulation.

Regarding this we have recently observed that patients with AF have about 20% prevalence of low (<0.9) ankle/brachial index, which is a marker of systemic atherosclerosis and it is associated with enhanced risk of ischemic stroke and myocardial infarction. These findings likely account for the coexistence of ischemic stroke of thrombo-embolic and atherosclerotic origin and for a rate of coronary heart disease which is almost similar to that of ischemic stroke. Hence, lowering the negative clinical impact of AF, particularly in the elderly patients, represents an important goal for the western countries whose aging population is rapidly growing. Clinically relevant advantages have been achieved by oral vitamin K antagonists, which reduce by >60% the risk of systemic thrombo-embolism and, more recently, by novel oral anticoagulants. Despite this success, patients with AF treated with novel oral anticoagulants or
warfarin still experience a residual risk of stroke and cardiac-related events.5.

Exploring new alternative approaches to mitigate thrombo-embolism in AF is, therefore, mandatory. In this context, radio frequency (RF) ablation of left atrium attracted the attention of many researchers as it appears a novel and interesting approach to reduce the burden of AF and to facilitate its management. Thus, restoration and maintenance of cardiac sinus rhythm by RF ablation has a positive impact on the vascular complications of AF and may reduce the need of anti-thrombotic treatment.

An important caveat associated with RF ablation is represented by asymptomatic cerebral emboli, which were previously detected in the early post-RF ablation period in up to 14% of patients.6,7. Technical procedures for RF ablation and AF-related clotting activation are implicated in this vascular complication.

Technical procedures employed for left atrium ablation have a key role in favoring asymptomatic cerebral emboli via either gas produced by air introduction in the sheaths or during heating/boiling of the blood or denaturation of tissue or blood components.8. A substantial reduction of asymptomatic cerebral emboli has been achieved by using a multi-electrode RF and by lowering the introduction of air into the left atrium during the catheter insertion and removal.7. Short- and long-term follow-up studies consistently documented a rate of ischemic stroke between 0.5 and 1.7%, which is much lower than that previously reported9,10.

Activation of clotting system is another critical issue, which is related with the duration of RF procedure and concurs to asymptomatic cerebral emboli.8,11. In this issue of Circulation Stazzi et al12 address the question as to whether platelet activation is also implicated in the pro-thrombotic state occurring after RF ablation and if remote ischemic pre-conditioning(IPC) is able to prevent it. The background to explore this issue was based on a previous study which
investigated the effect of warfarin in association with aspirin, an inhibitor of platelet thromboxane A$_2$ via COX1 acetylation, in 207 warfarin-treated AF patients undergoing left atrial ablation$^{13}$. Warfarin was discontinued 3 days before the procedure and substituted with aspirin at dosage of 325 mg o.d. without bridging to low-molecular weight heparin. Warfarin was restarted on the day of the procedure. Only two cases of transient ischemic attacks were registered after ablation, providing indirect evidence that platelets may be activated by ablation and suggesting that its inhibition by aspirin is safe and of potential clinical usefulness$^{13}$. To further substantiate the effect of RF ablation procedure on platelet function Stazzi and her colleagues included 19 consecutive patients with paroxysmal AF who were randomized to receive remote ischemic preconditioning (IPC; n=10) or sham intermittent ischemia (n=9) as control before RF ablation. Remote IPC was achieved by 3 short periods of forearm ischemia (5 minutes) by cuff sphygmomanometer inflation, separated by 5 minutes of reperfusion. The cuff of sphygmomanometer was inflated to a pressure value of 50 mmHg and 10 mmHg above the systolic blood pressure in the remote IPC group and the control group respectively. Platelet activation and reactivity were assessed by measuring monocyte-platelet aggregates and the expression of platelet receptors glycoproteins IIb/IIIa and P-selectin by flow cytometry in 4 different steps: before (1) and immediately after (2) forearm ischemia and immediately (3) and 24 hours after (4) RF ablation. Platelet biomarkers did not significantly differ in groups randomized to IPC or sham procedure in the first two steps of the protocol. Conversely, a significant increase of platelet biomarkers was detected in both groups immediately after RF ablation, which persisted until 24 hours after the procedure. However, a lower increase of platelet-leucocyte aggregates, as well as, of expression of IIb/IIIa and P-selectin on platelet surface was detected both at the end of ablation and 24 hours after the procedure in patients who
underwent remote IPC compared to those on sham procedure. This suggests that remote IPC was able to counteract platelet activation elicited by RF ablation. The novelty of the Stazzi’s study is that, using a standard procedure to perform ablation, platelets are over-activated but the mechanism underlying such phenomenon was not explored.

There are some clinical issues that should be addressed while analyzing these results. First, the report is essentially a pathophysiologic research and, as correctly underscored by the authors, underpowered to analyze the relationship between changes of platelet activation and asymptomatic cerebral emboli, an issue which should be investigated in the future. Second, platelet changes have been observed in a well selected population with no previous history of cardiovascular or cerebrovascular disease indicating that they included AF patients with relatively low CHA2DS2-VASc score. Analysis of platelet activation should, therefore, repeated in patients with higher CHA2DS2-VASc score to see if pre-existing vascular risk of AF undergoing RF ablation may have a different impact on platelet activation. In this context, it is of note that about 30% of patients included in the study were already on aspirin treatment, therefore it cannot be excluded that the negative impact of ablation on platelet activation could be even more relevant.

Another novelty of the study is that remote IPC, but not sham procedure, was able to attenuate platelet activation observed after RF ablation procedure. In particular Stazzi and her colleagues found less monocyte-platelet aggregates and lower expression of glycoprotein IIb/IIIa and P-selectin expression on platelet surface in patients who underwent remote IPC. This finding is in keeping with a previous study which analyzed if ischemic preconditioning affected thrombosis and markers of platelet activation in an experimental model of thrombosis. This study reported that ischemic preconditioning reduced experimental thrombosis and, similarly to
the Stazzi’s results, attenuated neutrophil-platelet aggregates and down-regulated platelet expression of glycoprotein IIb/IIIa and P-selectin

The mechanism through which remote IPC attenuates platelet response is still unclear and, at the moment, only a matter of speculation. Most hypothesized mechanisms focused on extracellular changes which in turn could negatively affect platelet activation. Among them, release of adenosine from peripheral tissues was hypothesized to have a role. In fact, adenosine, despite its short half-life, is able to elicit prolonged platelet inhibition via stimulation of adenosine A₂ receptors; however pharmacologic study in animals failed to support such hypothesis. Other extracellular mechanisms including release of prostacyclin or nitric oxide from endothelium are unlikely to be implicated due to the very short half-life of these molecules. Platelet refractoriness to the stimuli as a consequence of prolonged ischemia could also be implicated but in vitro experiments mimicking ischemia-reperfusion models would be against this hypothesis. Thus, platelets which undergo anoxia and then reoxygenated disclose a burst of reactive oxidant species. These species contribute to activating platelet aggregation via overproduction of the eicosanoids thromboxane A₂ and isoprostanes and down-regulation of nitric oxide generation. It cannot be excluded, however, that repeated shot of ischemia-reperfusion may result in an opposite effect and be associated with impairment of intra-platelet signaling of platelet activation but this point must be explored in the future.

Although Stazzi’s findings are of interest and could provide more insight in the mechanism accounting for thrombosis in AF patients undergoing RF ablation, they should be considered preliminary at the moment. Thus, further study should be addressed to explore the intra-signaling pathways implicated in platelet activation and, overall, to ascertain if RF ablation-induced platelet activation is or not associated with an increased risk of cerebral embolism. At
the moment, there is a general consensus that uninterrupted anticoagulation with warfarin is safe and not associated with bleeding complications; warfarin is recommended to be given about 30 days before the procedure and continued at least up to 3 months or lifelong depending on the severity of CHA2DS2-VASc SCORE\(^4\). However, this is a critical issue that has not been adequately addressed so far and randomized clinical trials are needed to clearly establish if, and in which patient’s category, anticoagulation should be continued over time.

In conclusion, following the current guidelines with the anticoagulant therapy with warfarin before and after ablation and optimizing intra-procedural anticoagulation with heparin to achieve an ACT >300 sec, bleeding risk and the rate of early and late cerebral embolism appear low\(^5\). Given the low residual risk of early and late thromboembolism with oral anticoagulants, it would be crucial to establish if the RF-induced platelet activation may be relevant in terms of cerebral embolism risk. Therefore, until a prospective study addressing this issue has not been done; inhibition of platelet activation by remote IPC or antiplatelet drugs before, during or after RF ablation seems to be premature.

**Conflict of Interest Disclosures:** None.

**References:**


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