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 that is facilitated by structural and functional changes elicited by atrial high-rate activity. The shortening of the atrial effective refractory period is the earliest functional change that characterizes atrial remodeling. As the 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 thromboembolic 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 experience cardiovascular events that occur as a consequence of the atherosclerotic disease. Thus, AF is typically associated with different risk factors of atherothrombosis, including hypertension, diabetes mellitus, and dyslipidemia and with systemic signs of atherosclerosis. This has been documented in the thoracic aorta and, more recently, in the peripheral circulation.\(^1\)

Regarding this we have recently observed that patients with AF have \(\approx 20\%\) prevalence of low (<0.9) ankle/brachial index, which is a marker of systemic atherosclerosis, and it is associated with an enhanced risk of ischemic stroke and myocardial infarction. These findings likely account for the coexistence of ischemic stroke of thromboembolic and atherosclerotic origin and for a rate of coronary heart disease that is almost similar to the rate of ischemic stroke.\(^2\) Hence, lowering the negative clinical impact of AF, particularly in 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 thromboembolism and, more recently, by novel oral anticoagulants.\(^3\) Despite this success, patients with AF treated with novel oral anticoagulants or warfarin still experience a residual risk of stroke and cardiac-related events.\(^4\)

Exploring new alternative approaches to mitigate thromboembolism in AF is, therefore, mandatory. In this context, radiofrequency (RF) ablation of the left atrium attracted the attention of many researchers, because it appears to be a novel and interesting approach to reduce the burden of AF and to facilitate its management. Thus, the 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 antithrombotic 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.\(^5,7\) Technical procedures for RF ablation and AF-related clotting activation are implicated in this vascular complication.

Technical procedures used 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 multielectrode 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 have consistently documented a rate of ischemic stroke between 0.5% and 1.7%, which is much lower than that previously reported.\(^9,10\)

The activation of the clotting system is another critical issue, which is related to the duration of the RF procedure and concurs to asymptomatic cerebral emboli.\(^8,11\) In this issue of Circulation, Stazzi et al\(^12\) address the question as to whether platelet activation is also implicated in the prothrombotic state occurring after RF ablation and if remote ischemic preconditioning (IPC) is able to prevent it. The background to explore this issue was based on a previous study that 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 once daily without bridging to low-molecular-weight heparin. Warfarin was restarted on the day of the procedure. Only 2 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. To further substantiate the effect of RF ablation procedures on platelet function,
Stazzi and her colleagues included 19 consecutive patients with paroxysmal AF who were randomly assigned 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 the sphygmomanometer was inflated to a pressure value of 50 mm Hg and 10 mm Hg 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 randomly assigned to IPC or sham procedure in the first 2 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-leukocyte aggregates, and of expression of IIb/IIIa and P-selectin on platelet surface, as well, was detected both at the end of ablation and 24 hours after the procedure. This suggests that remote IPC was able to counteract platelet activation elicited by RF ablation. The novelty of Stazzi’s study is that, with the use of a standard procedure to perform ablation, platelets are over-activated, but the mechanism underlying such a phenomenon was not explored.

There are some clinical issues that should be addressed while analyzing these results. First, the report is essentially pathophysiological research and, as correctly underscored by the authors, underpowered to analyze the relationship between changes of platelet activation and asymptomatic cerebral emboli, an issue that 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 a relatively low CHA2DS2-VASc score. Analysis of platelet activation should therefore be repeated in patients with a higher CHA2DS2-VASc score to see if a preexisting vascular risk of AF undergoing RF ablation may have a different impact on platelet activation. In this context, it is of note that 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 the platelet activation observed after the RF ablation procedure. In particular, Stazzi and her colleagues found fewer monocyte-platelet aggregates and lower expression of glycoprotein IIb/IIIa and P-selectin on the platelet surface in patients who underwent remote IPC. This finding is in keeping with a previous study that analyzed if ischemic preconditioning affected thrombosis and markers of platelet activation in an experimental model of thrombosis. The study reported that ischemic preconditioning reduced experimental thrombosis and, similarly to Stazzi’s results, attenuated neutrophil-platelet aggregates and downregulated 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 that in turn could negatively affect platelet activation. Among them, the 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, a pharmacological study in animals failed to support such a hypothesis. Other extracellular mechanisms, including the release of prostacyclin or nitric oxide from endothelium, are unlikely to be implicated because of 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 that undergo anoxia and then are 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 downregulation of nitric oxide generation. It cannot be excluded, however, that a repeated shot of ischemia-reperfusion may result in an opposite effect and be associated with impairment of intraplatelet 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, future study should be addressed to explore the intrasignaling pathways implicated in platelet activation and, overall, to ascertain if RF ablation-induced platelet activation is or is 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 ≥30 days before the procedure and continued at least up to 3 months or lifelong depending on the severity of CHA2DS2-VASc SCORE. 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 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 intraprocedural anticoagulation with heparin to achieve an activated clotting time of ≥300 s, bleeding risk and the rate of early and late cerebral embolism appear low. 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 been done, the inhibition of platelet activation by remote IPC or antiplatelet drugs before, during, or after RF ablation seems to be premature.

Disclosures

None.
References


Platelet Activation After Radiofrequency Ablation in Atrial Fibrillation: Is There Any Clinical Implication?
Francesco Violi and Pasquale Pignatelli

_Circulation_. 2014;129:5-7; originally published online November 25, 2013; doi: 10.1161/CIRCULATIONAHA.113.006927
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/1/5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/