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Peri-Procedural Corticosteroid use in Improving Outcomes Following Atrial Fibrillation Ablation: Back to Square One?

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Bilateral pulmonary vein (PV) isolation by catheter ablation has become an established therapy for highly symptomatic, drug refractory, paroxysmal atrial fibrillation (AF) [1, 2]. The efficacy of pulmonary vein isolation has improved over the years through refinement of procedural technique as well as improved ablation technology involving irrigated ablation, contact force sensing, and "single shot" ablation techniques such as cryo, laser, and multielectrode ablation catheters[1, 3-5]. However, durable pulmonary vein isolation has remained a significant challenge with increasing rates of pulmonary vein reconnection noted during long-term follow-up [6, 7]. Similarly, acute reconnections as well as early recurrences during the blanking period have been associated with reduced freedom from AF during follow-up[8]. With radiofrequency (RF) ablation, acute inflammation from the ablation lesions itself have been thought to have a major role in AF recurrences during the immediate peri-procedural period [9].

Several studies have noted that pro-inflammatory processes might play an important role in the initiation and maintenance of AF [10, 11]. Koyama and colleagues in 2009 showed that immediate recurrence of AF (within 3 days) after ablation was closely associated with an acute inflammatory process, as assessed by a high body temperature, elevated C-reactive protein (CRP) and signs of pericarditis. Interestingly, during the early post-ablation course (4-30 days), inflammatory markers were highest in patients with premature atrial contractions and non-sustained AF. Recurrence of AF within the first month after ablation independently predicted late AF recurrences during follow-up [9]. Multiple mechanisms, including ablation-induced local myopericarditis, local tissue edema resulting in gaps in the ablation line, and changes in action potential duration have been suggested as the link between ablation-induced inflammation and enhanced arrhythmogenecity during follow-up [9, 12].

Corticosteroids exert their anti-inflammatory effects by inhibition of the synthesis of all the known inflammatory cytokines. The findings linking ablation-related inflammation and AF recurrence, along with beneficial data on corticosteroids in preventing AF recurrence after cardiac surgery [13], led to several studies evaluating anti-inflammatory therapies in reducing recurrent AF following RF ablation. Koyama et al, in 2010, randomized 125 paroxysmal AF patients to receive placebo or corticosteroids (hydrocortisone [2 mg/kg IV] on day of PVI followed by oral prednisolone [0.5 mg/kg/day] for 3 days after the procedure). They measured body temperature and CRP levels to assess the anti-inflammatory response. The study showed that corticosteroid use decreased immediate and late recurrence of AF following PVI [14]. Another prospective study by Kim et al in 2015 showed that steroids reduced early AF recurrence post-ablation but had no impact on late recurrences [15]. In contrast, 3 nonrandomized case-control studies utilizing single dose of intravenous corticosteroids did not show any benefit in preventing early and late AF recurrence [16-18].

In this edition of the Journal, Iskander and colleagues report the results of the STEROID AF Study, a prospective, randomized, double-blind, placebo controlled trial that evaluated the efficacy of peri-procedural oral prednisone in preventing early and late AF recurrences in patients undergoing their first RF ablation (PV isolation) for symptomatic, paroxysmal AF [19]. All patients had failed at least one antiarrhythmic drug. A total of 60 patients were randomized 1:1 to oral prednisone (60 mg per day given the day before, the day of, and the day after the ablation procedure) or matching placebo. Inflammatory cytokines (IL-1, IL6, IL-8, and TNF-α) were measured at baseline as well as prior to, immediately after and 24 hours after ablation procedure. Patients were followed for one year with 30-day event monitoring at 3 months, 6 months, and 12 months. There were no significant adverse effects related to steroid use. Despite being started a day before ablation, oral prednisone did not have any beneficial effect on reducing acute PV reconnection during the procedure (36% vs. 23% in placebo group, p=0.39) and radiofrequency ablation times (56 ±11 vs. 51 ±13 min in placebo group, p=0.1). Peri-procedural prednisone did not reduce the incidence of early recurrence of AF during the blanking period (27% in steroid group vs. 17% in placebo group; p=0.347) as well as freedom from AF at 12 months of follow-up (60% vs. 70% in placebo group; p=0.417). In fact, there was a non-significant trend

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towards worse outcomes in the prednisone group. The levels of IL-6 and IL-8 were significantly lower in the steroid group post-ablation whereas no significant changes were seen in the levels of TNF-α and IL-1.

The authors concluded that peri-procedural prednisone, despite significant acute lowering of IL-6 and IL-8 immediately post-ablation, did not impact early and late AF recurrences. The STEROID-AF study differs from prior studies in the pre-procedural use of prednisone as well as serial measurements of inflammatory cytokine levels.

The strength of the STEROID AF study is its randomized, double-blind, placebo-controlled design, lending excellent validity to the results reported. Other strengths include serial measurement of specific inflammatory cytokine levels as well as three separate 30-day event monitoring during the 12 month period to assess for AF recurrence. However, in assessing the clinical implications of this study, several limitations should be considered. The sample size is small and the statistical power to assess outcomes is not reported. Therefore, as the authors rightly reported, it is likely that the study may have been underpowered to assess the outcome variables. This is especially important given the fact that there was a trend towards worse outcomes in the steroid group and further exploration of this in a larger sample would have been useful.

Given significant difference in outcomes between studies evaluating steroid use in AF ablation, the specific role of peri-procedural inflammation in affecting short and long-term outcomes post-ablation is brought into question. The STEROID AF study clearly shows that prednisone reduced cytokine levels but that did not lead to improved ablation success. Thus, the mechanisms by which steroid use affects AF ablation outcomes remain unclear. It is possible that the beneficial effects of steroids in reducing cytokine levels may be offset by inhibition of adequate scar formation following ablation, allowing recovery of PV conduction. Also important will be to assess for any differences between the type of corticosteroid used, dosing and route of delivery. Whether other ablation modalities such as cryoablation and laser ablation have similar association with inflammation as RF ablation needs further study.

Interestingly, at 24 hours after ablation, the levels of IL-6 and IL-8 show a significant increase, compared to immediate pot-ablation levels, in both placebo and steroid groups. One would suspect that there was only a transient suppression of inflammatory cytokines followed by 'rebound' to level much higher than baseline and wonder whether 3 days of oral steroids may be enough for sustained suppression of inflammation; perhaps a longer course of anti-inflammatory therapy is needed, and may explain the beneficial effects from a 3-month course colchicine when used in a similar clinical situation [20].

The STEROID-AF data is a welcome addition to the debate on the role of inflammation in the early and late recurrence of AF following RF ablation as well as the appropriate role, if any, as well as the type and dose of corticosteroids in this population. It may be fair to say that we are back to square one. We have more data now and more is needed before we can put this debate to rest in our continuing quest to improve ablation success in AF patients.

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Disclosures

continuing quest to improve ablation success in AF patients.

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