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Colchicine for Prevention of Post-Operative Atrial Fibrillation: A New Indication for a Very Old Drug?

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Atrial fibrillation following cardiac surgery (post-operative AF, POAF) is a common problem, affecting 10-50% of all cardiac surgery patients, with the risks of POAF increasing as a function of patient age and the complexity of the surgery performed. POAF is associated with increased length of hospital stay, increased risk of comorbid conditions, and increased risk of mortality. As surgeries which do not directly manipulate the heart (lung resection, etc.) are also associated with POAF[1], it is clear that factors beyond atrial trauma and ischemia have a significant role in the development of POAF. Among these, surgery-related pericardial inflammatory processes, autonomic disturbance, and changes in plasma volume regulation are plausible mechanisms.

Many different drug classes have been evaluated for their potential to lower the incidence of POAF (amiodarone, statins, ACE-inhibitors, omega-3 fatty acids, antioxidants, etc.), but few if any of these agents have efficacy supported by the results of randomized, multi-center, double-blind, placebo-controlled clinical trials. In this issue of Circulation, Imazio and colleagues present a sub-study[2] of the recently completed COPPS trial[3], a randomized multicenter trial in which the prophylactic use of colchicine (initiated on post-operative day 3) was evaluated. The primary endpoint of the COPPS study was a reduction of the incidence of post-pericardiotomy syndrome (PPS, characterized by pleuritic chest pain, friction rub, pleural and pericardial effusions). As a secondary endpoint, the authors evaluated the impact of treatment on the combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis and relapses. Colchicine demonstrated efficacy for both the primary endpoint (reduction of PPS from 21.1% to 8.9%, p=0.002) and secondary endpoint (0.6% vs. 5.0%, p=0.024)[3].

In the current POAF sub-study[2], Imazio and colleagues have assessed the impact of colchicine treatment on the incidence of POAF occurring between post-operative day 3 (after treatment onset) and 1 month after surgery. In their analysis, increased left atrial size, surgery other than CABG and presence of pericardial effusion were associated with increased risk of POAF; in contrast, use of perioperative beta-blockers and colchicine treatment were protective. Baseline characteristics of the control and colchicine treated patient groups were balanced, but the patients on colchicine had a reduced incidence of

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POAF (12.0% vs. 22.0%, p=0.021), with a shorter in-hospital stay (p=0.04) and shorter stay in rehabilitation (p=0.009). There was no difference in the incidence of death or stroke (1.2% in both groups), and side effects were similar in the control- and placebo-treated groups. These results are promising and suggest that colchicine may be useful in the prevention of POAF. However, as acknowledged by the authors, there are some important caveats. In this study, 43% of the POAF episodes documented occurred before the onset of colchicine treatment. As the study drug was not initiated until post-operative day 3, it is unclear if colchicine would be equally effective in suppressing the earlier episodes of AF. Clinical studies have shown that the peak incidence of AF occurs on postoperative days 2-3, a time that is well correlated with the peak of plasma levels of C-reactive protein (CRP), an acute phase reactant and sensitive marker of systemic inflammation [4]. Circulating white cell counts are frequently elevated in patients that experience postoperative atrial fibrillation[5]. Imazio and colleagues have not reported the impact of colchicine treatment on either plasma CRP levels or leukocyte counts.

In animal studies, experimental sterile pericarditis (created with epicardial application of talc and gauze) has been used to create a reliable substrate for the induction of atrial fibrillation and atrial flutter [6]. In this model, treatment with prednisone lowered postoperative plasma C-reactive protein levels, decreased pericardial adhesions, and significantly attenuated the inducibility of AF on post-operative days 3-4 [7]. Histologic analysis revealed a reduction of neutrophil infiltration and epicardial injury [7]. Experimental sterile pericarditis is characterized by profound epicardial neutrophil infiltration which promotes gap junction remodeling. Areas with significant neutrophil infiltration displayed necrotic changes and had a lower abundance of connexins 40 and 43 [8].

Consistent with this observation, atrial myeloperoxidase (MPO) levels (which reflect neutrophil/macrophage infiltration) were associated with conduction slowing and conduction heterogeneity in another canine cardiac surgery model[9]. In this model as well, prednisone attenuated atrial myeloperoxidase levels, changes in conduction pattern and velocity, and the inducibility of AF[9]. MPO is an oxidant generating enzyme that consumes nitric oxide. MPO promotes matrix metalloproteinase activity, oxidant generation, fibroblast proliferation and extracellular matrix production (interstitial atrial fibrosis) – important elements of the substrate for atrial fibrillation. In a translational study, it was observed that whereas control mice infused with angiotensin-II developed extensive leukocyte infiltration, atrial fibrosis and had inducible AF, MPO-deficient knockout mice developed less fibrosis and were protected from AF[10].

Plant extracts containing colchicine have been used to treat gout-associated arthritis for nearly 4000 years [11], and gout remains the primary indication for the use of colchicine. Colchicine blocks microtubule assembly and can actively disrupt microtubules. Microtubules have a significant role in numerous cellular cytoskeletal and intracellular transport activities. One of the most potent effects of colchicine (at nanomolar concentrations) is a suppression of a chemotactic factor from neutrophil lysosomes[11]. As a result, colchicine attenuates neutrophil activation, endothelial cell adhesion and migration to injured tissues[11]. On the basis of the above preclinical studies and insights into the biologic activity of colchicine, it is not unexpected that colchicine, an agent with potent anti-inflammatory activity, may have a significant anti-arrhythmic effect in post-surgical patients.

In addition to the potential effects of colchicine on neutrophil activation/migration/ infiltration, colchicine may have relevant effects on atrial myocytes. Microtubules regulate the localization and interaction of adrenergic receptors and adenylate cyclase in caveolae (specialized lipid domains in the cell membrane)[12]. As a result, microtubules modulate the

phosphorylation of calcium channels[13] and likely affect the response of the atria to autonomic stimulation. As autonomic balance is altered in the postoperative state[14], agents which attenuate sympathetic activity (eg., beta-adrenergic receptor blockers or colchicine) or increase parasympathetic activity may decrease the risk of calcium overload induced ectopy that contributes to the initiation of POAF.

POAF has important clinical consequences (including increased risk of stroke and other embolic conditions) and is associated with a significant economic burden on the health care system[15, 16]. The results of the post-hoc substudy presented in this issue by Imazio and colleagues are promising. It will be of great interest for the authors or others to prospectively evaluate the utility of perioperative colchicine treatment (beginning at the time of surgery or before) as a prophylactic approach that can reduce the morbidity associated with this very common post-surgical complication. If colchicine is effective in preventing postoperative atrial fibrillation, this treatment would constitute an important new indication for the use of a very old drug.

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