ArrhythmiaNews

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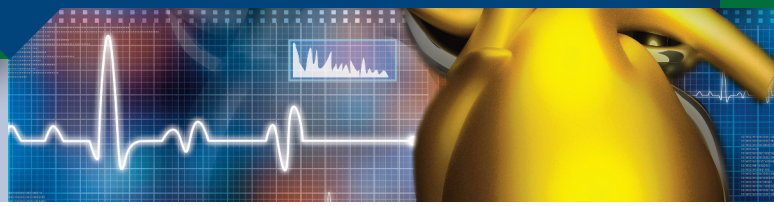

Botulinum Toxin:
An Exciting New Antiarrhythmic Intervention

Atrial fibrillation (AF) is a common complication after cardiac surgery occurring in 30 to 60% of patients. Postoperative AF is associated with longer hospital stays, increased health care costs, greater stroke risk, and higher mortality.

Postoperative AF has remained a stubborn clinical problem for decades with no consistently effective therapeutic approach.

The autonomic nervous system, including both parasympathetic and sympathetic components, plays an important role in the genesis of atrial fibrillation in all contexts, but particularly in the postoperative environment. The cardiac autonomic ganglionic plexi contain a rich network of fibers that innervate the atria and play an important role in modulating atrial electrophysiologic properties. Targeting these ganglionic plexi via catheter ablation has yielded mixed results but suggests that effective ablation can yield at least incremental benefits in some subsets of patients.

Botulinum toxin (BTX) is a potent inhibitor of cholinergic neurotransmission that can cause local and temporary neuromodulation or chemodenervation when injected into target tissue. BTX type A binds to presynaptic cholinergic nerve terminals and blocks synaptic exocytosis of neurotransmitters. It is effective in a variety of local neural tissues including autonomic nerves, and is FDA approved for a variety of neurologic and cosmetic indications. But it is important to note that in animal models, it has also produced suppression of spontaneous or induced atrial fibrillation without any adverse effects.

We performed a randomized placebo-controlled doubleblind pilot study in 2015, of 60 patients undergoing open-heart coronary artery bypass graft surgery (CABG).[1] Patients either received BTX injection into four posterior epicardial fat pads containing the dominant atrial neural ganglia or received a placebo. The control group had the anticipated 30% incidence of postoperative AF within 30 days of surgery. The BTX group had a dramatic reduction in postoperative AF with an incidence of only 7% (P = 0.024).

A recent larger study at Duke University randomized 130 patients undergoing CABG and/or valve surgery and observed a borderline significant 30% relative risk reduction of postoperative AF in the BTX group. No safety issues were identified.

All 60 patients continued follow-up as part of a formalized analysis of long-term outcomes in

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our randomized clinical trial and AF events were tracked by implantable loop recorders in all patients.[2] Between 30 days and up to the 12-month follow-up examination, 7 of the 30 patients in the placebo group (27%) and none of the 30 patients in the BTX group (0%) had recurrent AF (P = 0.002). BTX injection induced pronounced alteration of heart rate variability (HRV) components for about 6 months, suggesting reduction of both parasympathetic and sympathetic activity. Despite the finding that HRV changes dissipated in 6 months, we observed the very intriguing observation that BTX injection was associated with a lower AF burden during 1-year follow-up.

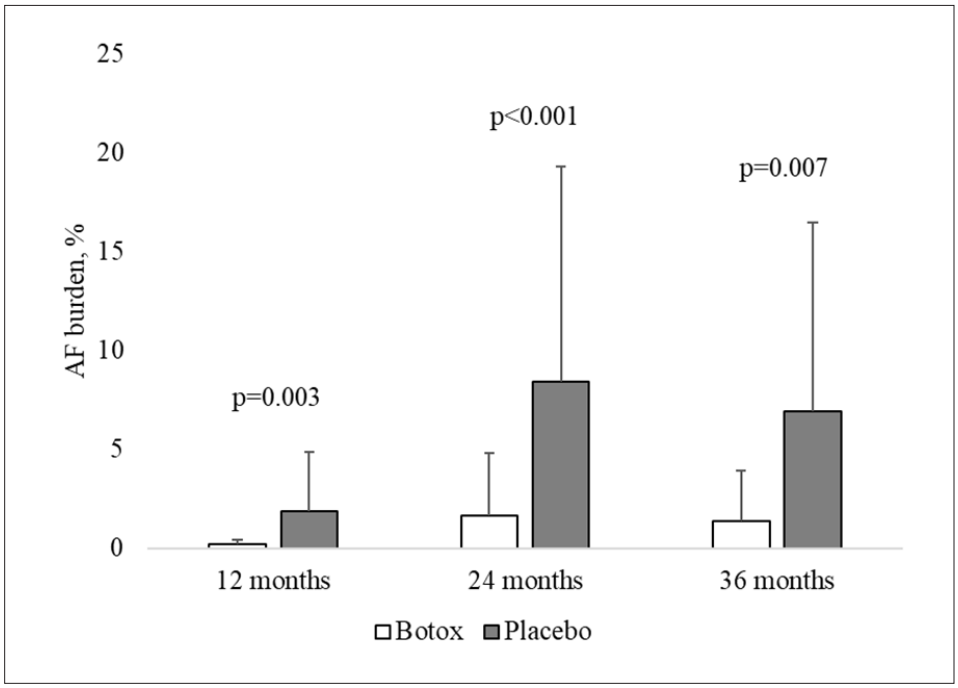

Figure 1: AF burden based on implantable loop recorder during long-term follow-up after BTX injection during CABG.

At the end of 36 months, the incidence of any atrial tachyarrhythmia was 23.3% in the BTX group as compared to 50% in the placebo group (HR 0.36, P = 0.02).[3] The mean AF burden at 12, 24 and 36 months was significantly lower in the BTX group compared to the placebo group: 0.22% vs 1.88% (P = 0.003), 1.6% vs 9.5% (P < 0.001) and 1.3% vs 6.9% (P = 0.007) (see *Figure 1*), respectively. In the BTX group, 2 (7%) patients were hospitalized during follow-up compared to 10 (33%) in the placebo group (P = 0.02).

The consistent results indicated that BTX injection into epicardial fat pads during CABG resulted in a sustained substantial reduction of atrial tachyarrhythmia incidence and AF burden during 3-year follow-up, accompanied by reduction in hospitalizations. This was and is a puzzling but intriguing observation that may have important mechanistic and therapeutic implications. It may simply be a result of reverse atrial remodeling following reduction in short-term AF burden that helps "reset" the predisposition to AF. Alternatively, BTX inhibits the release of acetylcholine and thus reduces atrial cholinergic neurotransmission. Hyperactivity of the cardiac autonomic nervous system plays an important role in triggering AF, and the development of AF further augments local autonomic activity, creating a potential vicious cycle. It is conceivable that temporary interruption of hyperactivity of the local cardiac nervous system input by BTX could break the vicious cycle and yield a sustained therapeutic effect. Experimental support for this hypothesis was provided in a

recent elegant study by Lo et al.[4] In anesthetized dogs, BTX temporarily lengthened atrial refractory period which when retested at 3 months had returned to baseline consistent with its expected temporary effect. However, BTX administration also greatly diminished AF induced by rapid atrial pacing throughout the 3-month study protocol and prevented parasympathetic hyperinnervation at the ganglionic plexi and sympathetic hyperinnervation at the atrial myocardium, compared to controls. The authors believed that the findings indicated that "autonomic remodeling plays a crucial role in the progression of AF and that suppression of autonomic remodeling may prevent electrical remodeling and subsequently prevents AF from perpetuating itself." We endorse this concept as a very plausible explanation for the long-term AF suppression by BTX observed in our studies, and look forward to further experimental and clinical investigation.

Based on these exciting findings, Dr. Steinberg has been working with Allergan, Inc. on the design of future cardiac studies of BTX. Allergan is the major pharmaceutical industry leader in BTX clinical use. In early 2019, Dr. Steinberg will lead a team of investigators in a multi-center, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to evaluate the efficacy and safety of BTX type A injections into the epicardial fat pads, foci of ganglionic plexi, to prevent postoperative AF in patients undergoing open-chest cardiac surgery. It is projected that a total of approximately 20 to 30 sites in North America and Europe will enroll a total of approximately 330 participants for this phase 2 study. Results are expected in early 2020.

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SMG electrophysiologists are appointed to faculty of Seton Hall-Hackensack Meridian School of Medicine

Dr. Steinberg is the Core Professor of Cardiology and Internal Medicine, and Dr. Altman is the Assistant Professor of Cardiology and Internal Medicine, as part of the inaugural faculty at the new medical school at Seton Hall.

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