

Cardiac Autonomic Disorders and Botulinum Toxin Treatment

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Introduction

Botulinum toxin, which has a zinc-binding metalloendopeptidase function, is a bacterial endotoxin produced by *Clostridium botulinum* during growth and reproduction. Botulinum toxin acts at the neuromuscular junction and autonomic preganglionic and parasympathetic postganglionic neurons to inhibit the exocytotic release of acetylcholine stored in synaptic vesicles [1]. Therefore, botulinum toxin blocks cholinergic neurotransmission at the neuromuscular junction and autonomic nerve endings, which is important for motor function and autonomic neuronal activity especially parasympathetic activity. Recently, botulinum toxin was established as a highly effective and safe treatment option for movement disorders (focal dystonias, focal spasticity, essential tremor, etc.) and autonomic disorders (focal hyperhidrosis, hypersalivation, hyperactive bladder, etc.) [2-3]. Interestingly, botulinum toxin has a markedly longer duration of action in autonomic than in motor disorders [4-5], suggesting that it is more effective for the treatment of autonomic disorders than motor disorders.

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It is well-known that autonomic nerves intensively and asymmetrically innervate the heart and regulate the cardiac function [6]. In particular, unbalanced activation of cardiac autonomic nerves may induce cardiac rhythm disturbance such as bradycardia and tachyarrhythmia. At the beginning of this century, however, there was no available data on whether botulinum neurotoxin inhibits parasympathetic ganglionic neurotransmission in the heart, although botulinum toxin as a clinical drug inhibits the release of acetylcholine at the neuromuscular junction. As the preganglionic parasympathetic nerve endings are primarily located in the epicardial and endocardial fat pads (i.e., ganglionated plexi) close to the heart, we examined the effects of botulinum toxin on parasympathetic ganglionic activation and demonstrated that the selective injection of botulinum toxin into the sinoatrial fat pad blocked bradycardia induced by parasympathetic ganglionic activation in dog hearts [7]. Moreover, we also demonstrated that successive conditioning low-frequency cervical vagal stimulation accelerated botulinum toxin-induced inhibition of the bradycardia induced by vagal stimulation, suggesting that botulinum toxin treatment might be more effective in the setting of increased vagal tone. The existence and location of epicardial fat pads in the human heart is known to be similar to those of the canine heart [8]. Moreover, targeting cardiac autonomic ganglia by fat pad ablation has been shown to effectively suppress atrial fibrillation [9]. Therefore, botulinum toxin may be a highly effective and safe treatment option for parasympathetic mediated atrial fibrillation and other diseases that are aggravated by parasympathetic activation in a clinical setting. In fact, recent clinical and experimental studies demonstrated that fat pad ablation by botulinum toxin is effective for the inhibition of atrial fibrillation. For example, Oh et al. [10] demonstrated that the injection of botulinum toxin into the sinoatrial and atrioventricular fat pads suppressed vagally-mediated atrial fibrillation for at least 1 week with a reduced dispersion of the effective refractory period in mongrel dogs. Moreover, botulinum toxin injection into 4 epicardial fat pads

Sl.No	Summary
1	Botulinum toxin injection into cardiac epicardial fat pads suppresses post-cardiac operation- and vagally-mediated atrial tachyarrhythmias without any serious adverse events.
2	Selective injection of botulinum toxin into the sinoatrial fat pad can block vagally-mediated-bradycardia especially in the setting of increased vagal tone.
3	Botulinum toxin may be a highly effective and safe treatment option for autonomically-mediated atrial fibrillation and other diseases that are aggravated by parasympathetic activation in a clinical setting.

Table 1: Summary of botulinum toxin treatment for cardiac autonomic disorders.

provided atrial tachyarrhythmia suppression during a year without any serious adverse events in humans [11]. However, longer-term effects of botulinum toxin treatment on atrial fibrillation suppression remain unclear. Moreover, partial atrial vagal ablation has facilitated rather than prevented the initiation of vagally mediated atrial fibrillation [12] (Table 1). We need to conduct further studies on the effectiveness of botulinum toxin treatment to suppress atrial fibrillation to answer the questions. Finally, we hope the broad possibilities of botulinum toxin are realized in the treatment of several autonomic disorders, including cardiac autonomic disease.

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