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  **Neuronally released vasoactive intestinal polypeptide alters atrial electrophysiological properties and may promote atrial fibrillation**

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## Background

Vagal hyperactivity promotes atrial fibrillation (AF), which has been almost exclusively attributed to acetylcholine. Vasoactive intestinal polypeptide (VIP) and acetylcholine are neurotransmitters co-released during vagal stimulation. Exogenous VIP has been shown to promote AF by shortening action potential duration (APD), increasing APD spatial heterogeneity, and causing intra-atrial conduction block.

## Objective

The purpose of this study was to investigate the effects of neuronally released VIP on atrial electrophysiologic properties during vagal stimulation.

## Methods

We used a specific VIP antagonist (H9935) to uncover the effects of endogenous VIP released during vagal stimulation in canine hearts.

## Results

H9935 significantly attenuated (1) the vagally induced shortening of atrial effective refractory period and widening of atrial vulnerability window during stimulation of cervical vagosympathetic trunks (VCNS) and (2) vagal effects on APD during stimulation through fat-pad ganglion plexus (VGPS). Atropine completely abolished these vagal effects during VCNS and VGPS. In contrast, VGPS-induced slowing of local conduction velocity was completely abolished by either VIP antagonist or atropine. In pacing-induced AF during VGPS, maximal dominant frequencies and their spatial gradients were reduced significantly by H9935 and, more pronouncedly, by atropine. Furthermore, VIP release in

the atria during vagal stimulation was inhibited by atropine, which may account for the concealment of VIP effects with muscarinic blockade.

#### Conclusion

Neuronally released VIP contributes to vagal effects on atrial electrophysiologic properties and affects the pathophysiology of vagally induced AF. Neuronal release of VIP in the atria is inhibited by muscarinic blockade, a novel mechanism by which VIP effects are concealed by atropine during vagal stimulation.

#### Abbreviations

**ACh**, acetylcholine; **AERP**, atrial effective refractory period; **APD**, action potential duration; **AVW**, atrial vulnerability window; **CV**, conduction velocity; **DF**, dominant frequency; **GP**, ganglionated plexus; **LA**, left atrium; **LAA**, left atrial appendage; **RA**, right atrium; **RAA**, right atrial appendage; **VCNS**, vagal stimulation through cervical vagosympathetic trunks; **VGPS**, vagal stimulation through ganglionated plexus; **VIP**, vasoactive intestinal polypeptide

#### Keywords

Vagal stimulation; Atrial fibrillation; Vasoactive intestinal polypeptide

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