Oscillatory ACh Release Impact on f-Wave Frequency Modulation: an Experimentally-Based Computational Study

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Parasympathetic neurotransmitter acetylcholine (ACh) shortens action potential duration in a dose dependent manner, which facilitates atrial fibrillation (AF) by reducing wavelength for reentry. Dominant f-wave frequency, F_f, exhibits significant variation, ΔF_f, and previous studies suggest that some of this variation relates to respiratory modulation. In this study, we tested the hypothesis that this could be related to [ACh] release pattern.

Electrocardiograms were recorded from seven patients during controlled respiration, before and after injection of atropine (ACh inhibitor), from which f-wave frequency modulation was characterized. Experimentally-based electrophysiological simulations in 2D human atrial tissue were performed to assess the effects of [ACh] release pattern on F_f. To mimic AF substrate, electrophysiological remodeling and 20% diffusive fibrosis were simulated. A cross-stimulation protocol was applied onto the tissue to initiate a rotor while cyclically varying [ACh] following a sinusoidal waveform of frequency equal to 0.125 Hz. Different mean levels (0.05, 0.075 μM) and peak-to-peak ranges (0.1, 0.05, 0.025 μM) of [ACh] variation were tested.

In all patients, an f-wave frequency modulation could be observed. In 57% of the patients, this modulation was significantly reduced after injection of atropine, supporting our hypothesis of a relationship with ACh release. From the simulations, we confirmed that rotor frequency variations followed the induced [ACh] patterns. The mean frequency of the rotor was dependent on mean [ACh] level, while the magnitude of frequency variation was dependent on [ACh] variation range (see Table). An [ACh] variation of 0.025 μM around a mean value of 0.05 μM was the one providing results closer to those measured from the patients.

In conclusion, the pattern of [ACh] release could be an important factor involved in f-wave frequency modulation. Further studies to understand the contribution of other factors and to ascertain whether [ACh] variations could be monitored from f-wave analysis are needed.

[ACh] release 0,125 Hz		**Range (peak-to-peak) of [ACh]**				**Mean values from patients**	
Mean [ACh]		**0,00**	**0,025**	**0,050**	**0,100**		
0,05 μM	$\overline{F_f}$	7,31	7,23	7,19	6,93	$\overline{F_f}$	6,82
	ΔF_f	0,02	0,23	0,50	1,29		
0,075 μM	$\overline{F_f}$	7,88	7,86	7,76		$\overline{\Delta F_f}$	0,15
	ΔF_f	0,02	0,25	0,43			