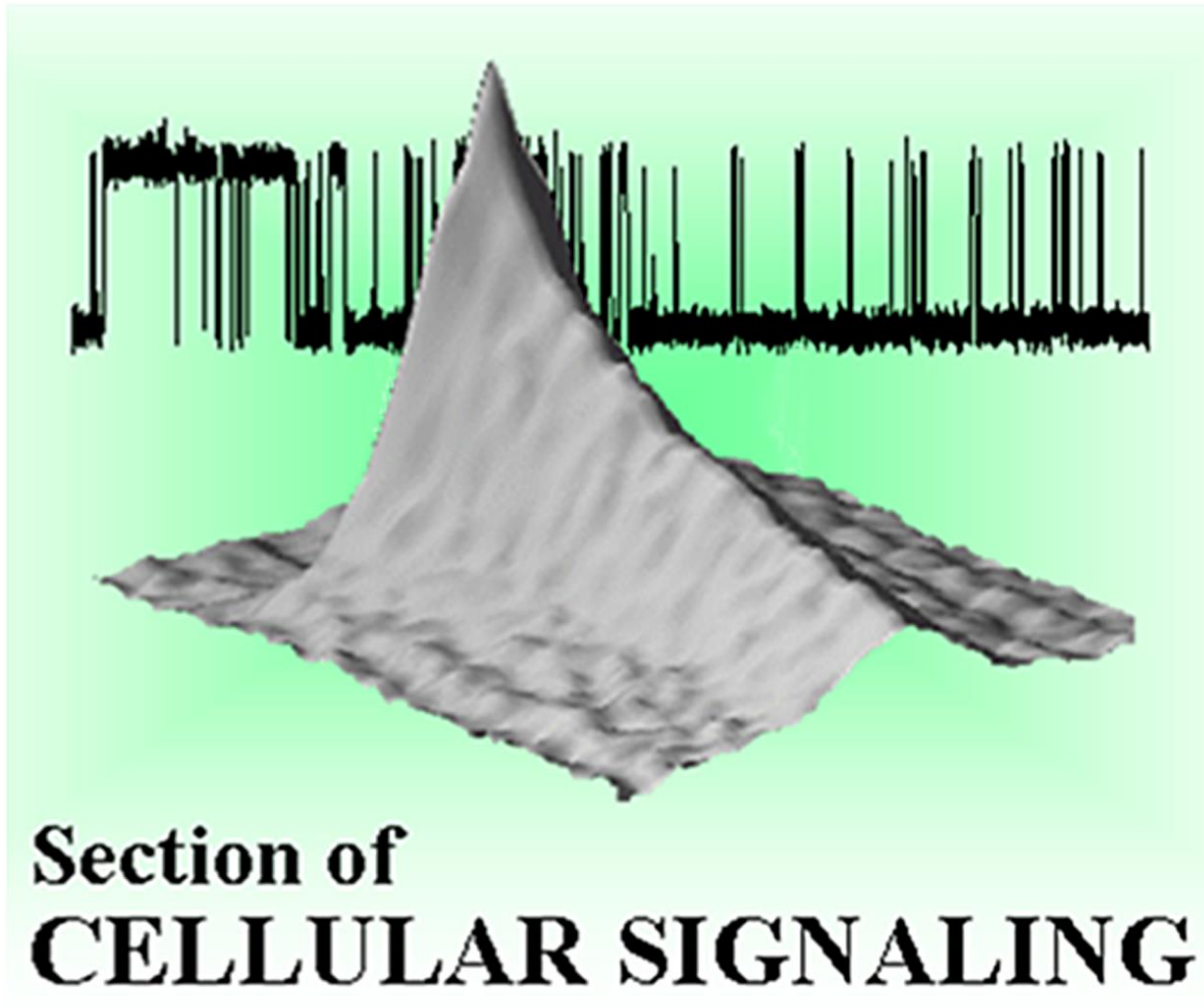


Action potential shortening prevents atrial calcium alternans



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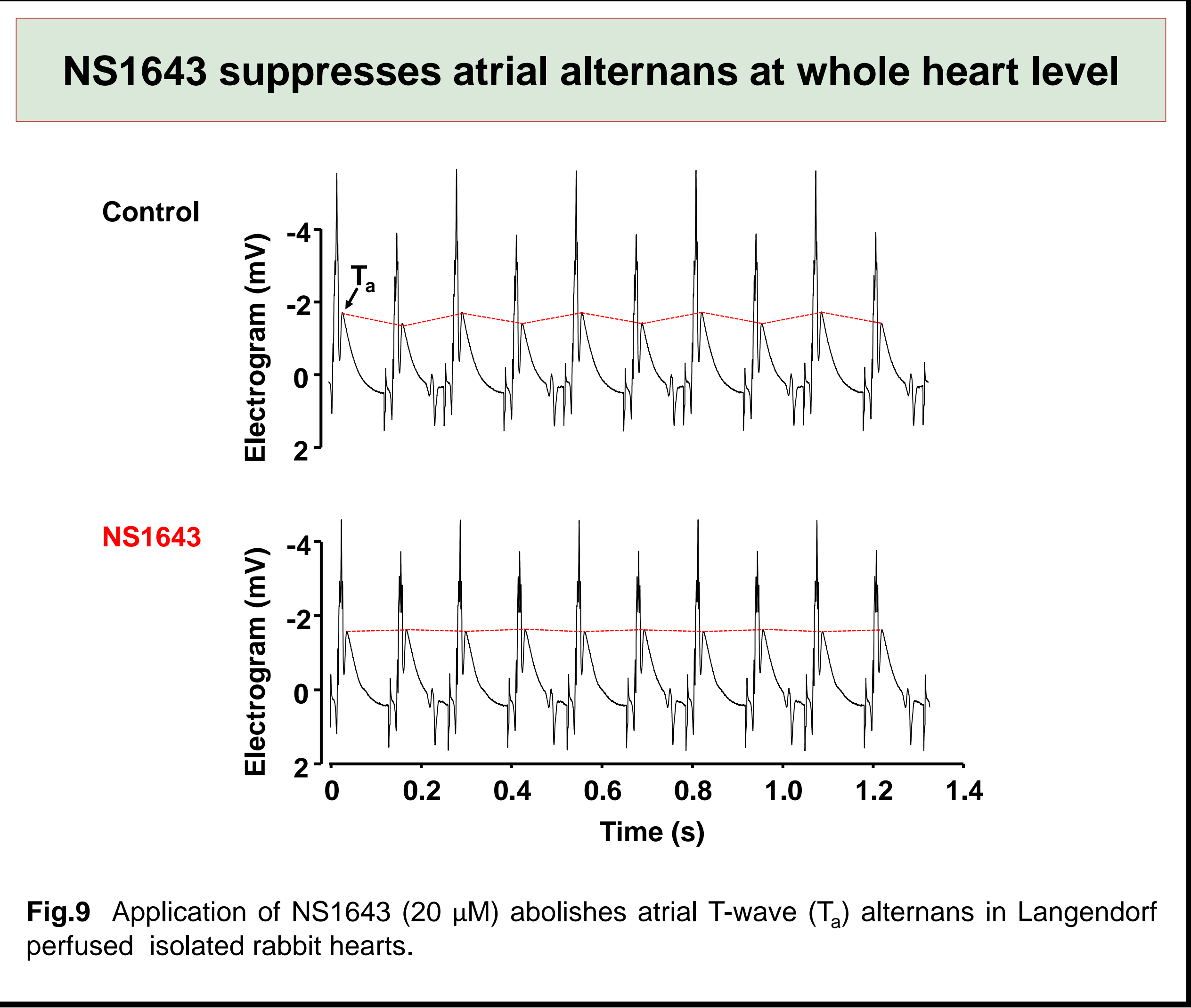
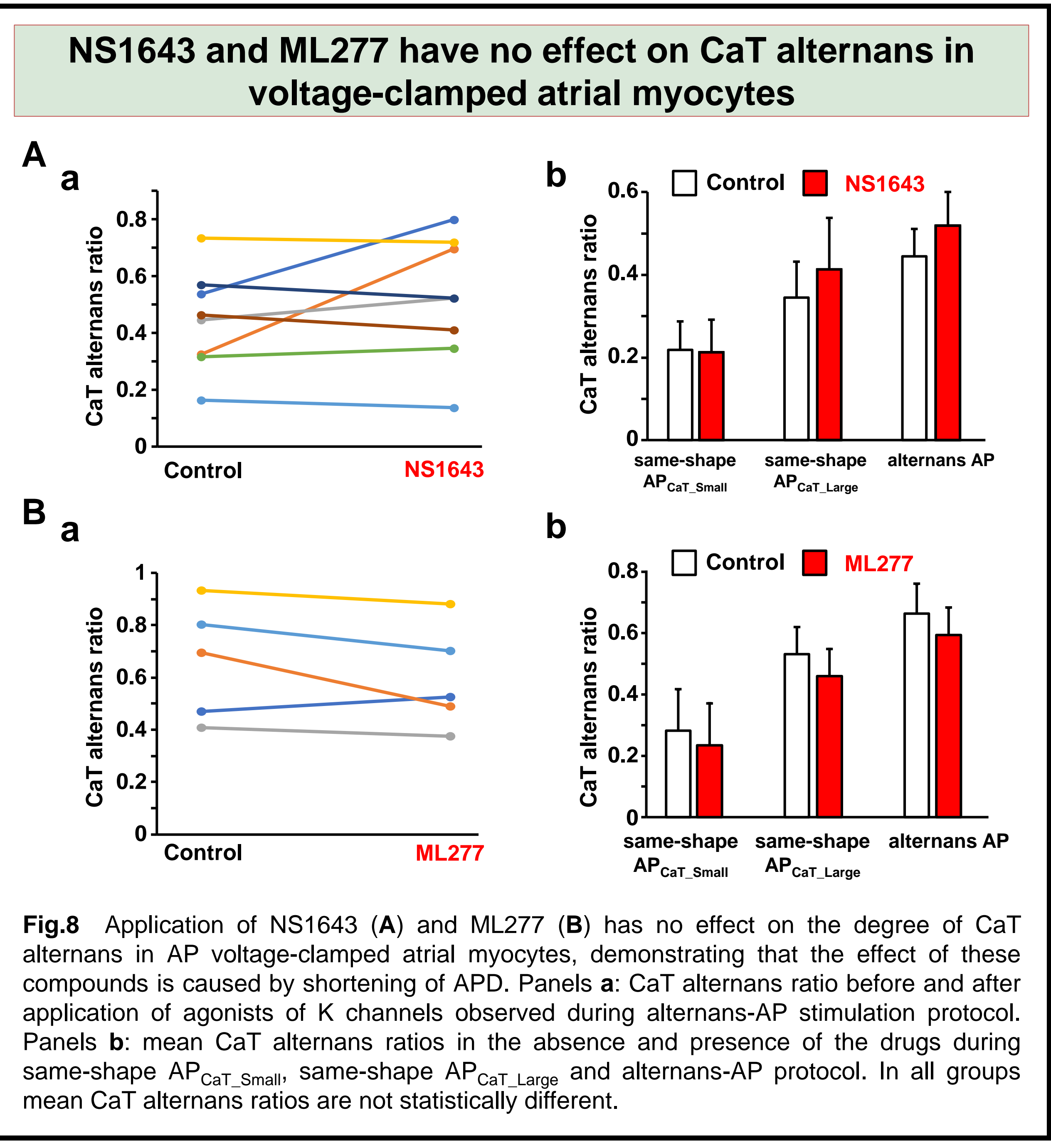
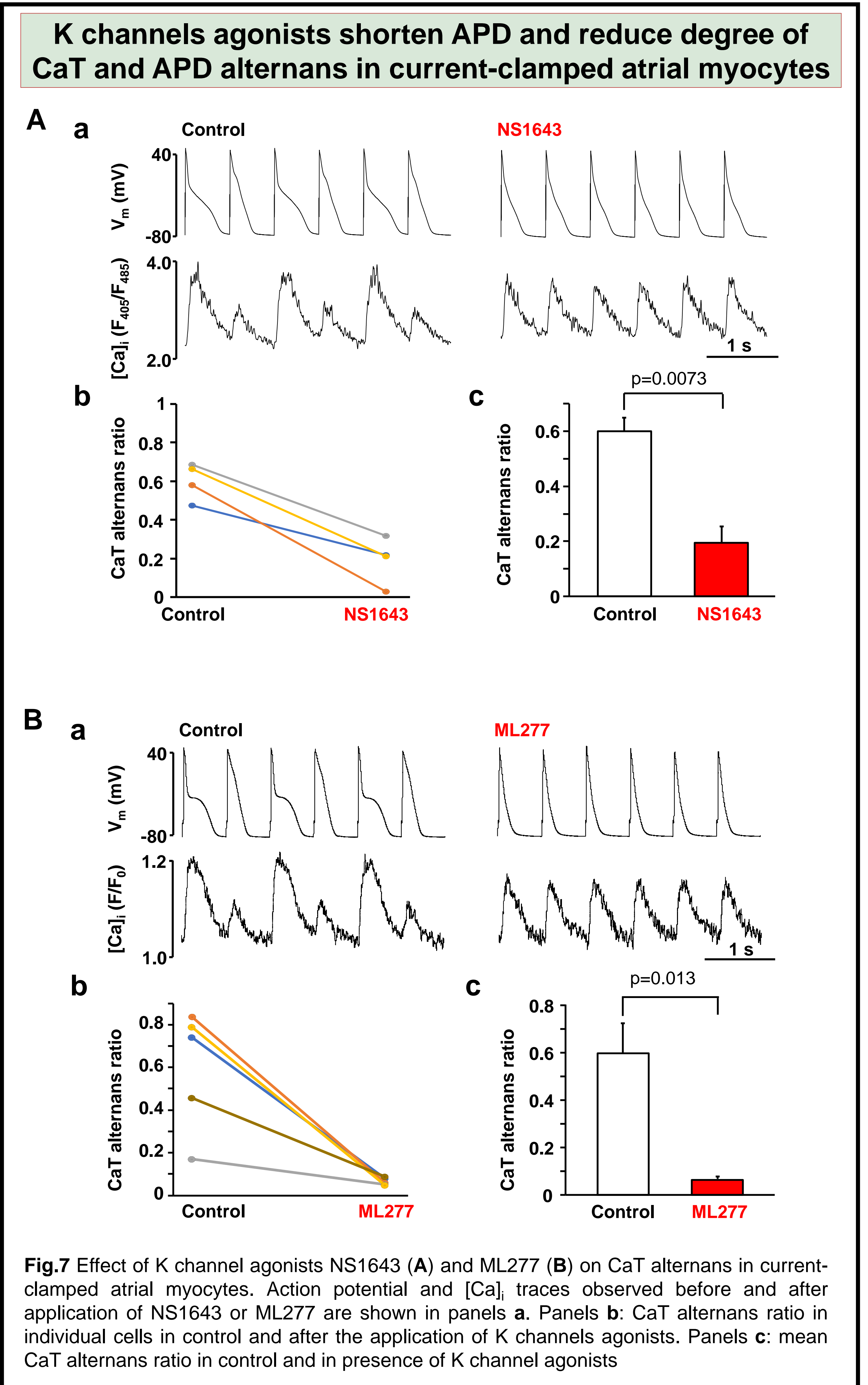
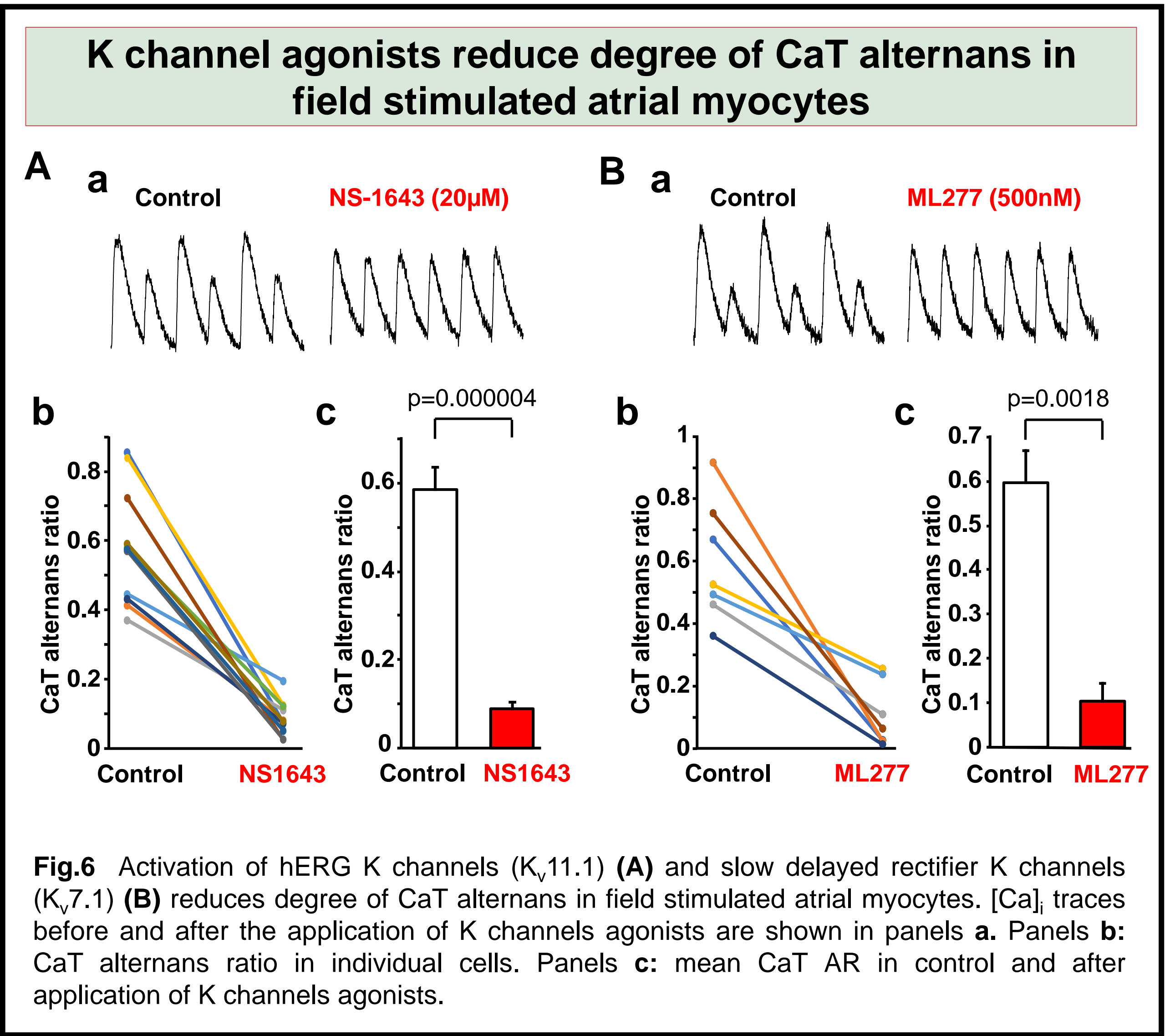
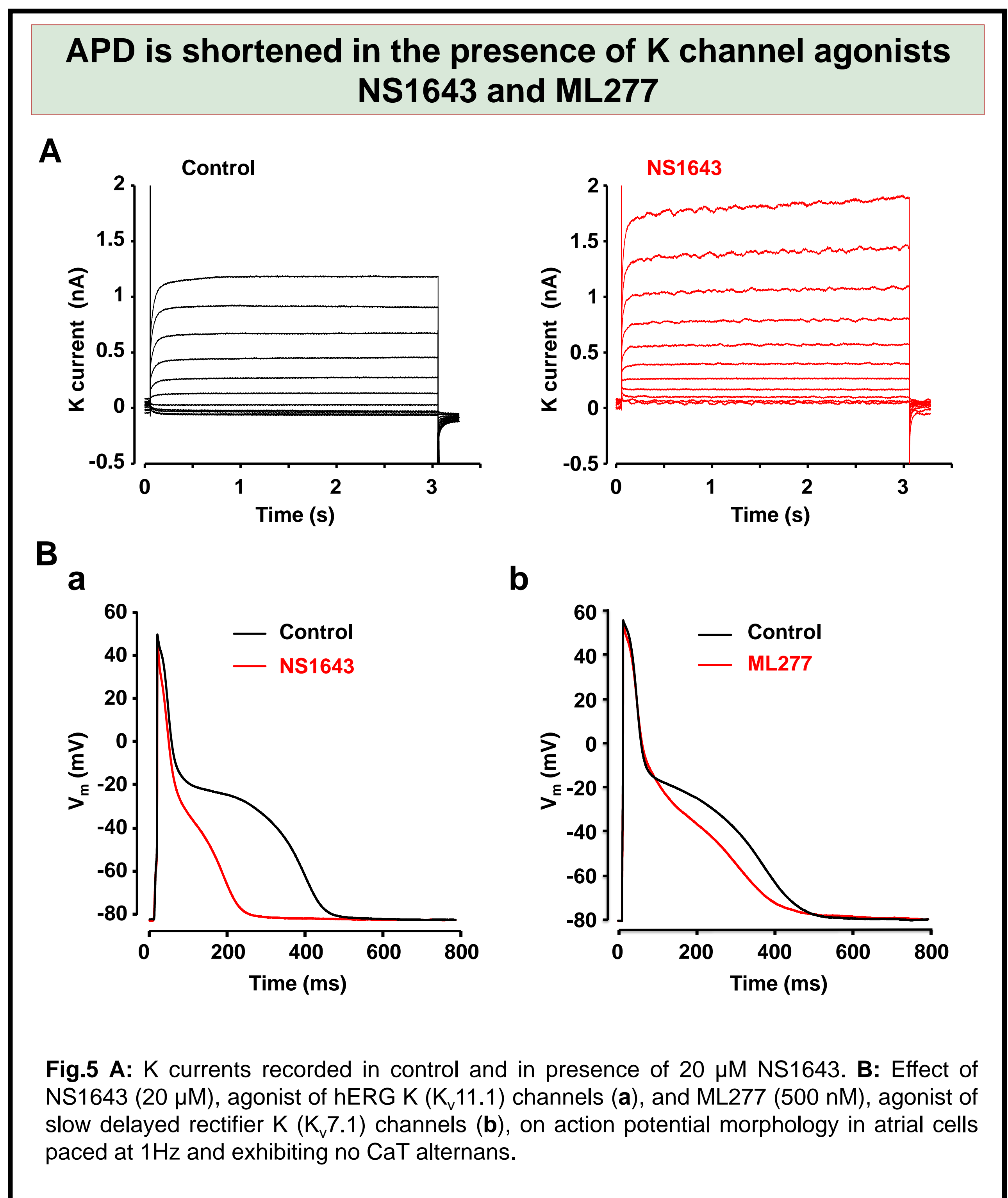
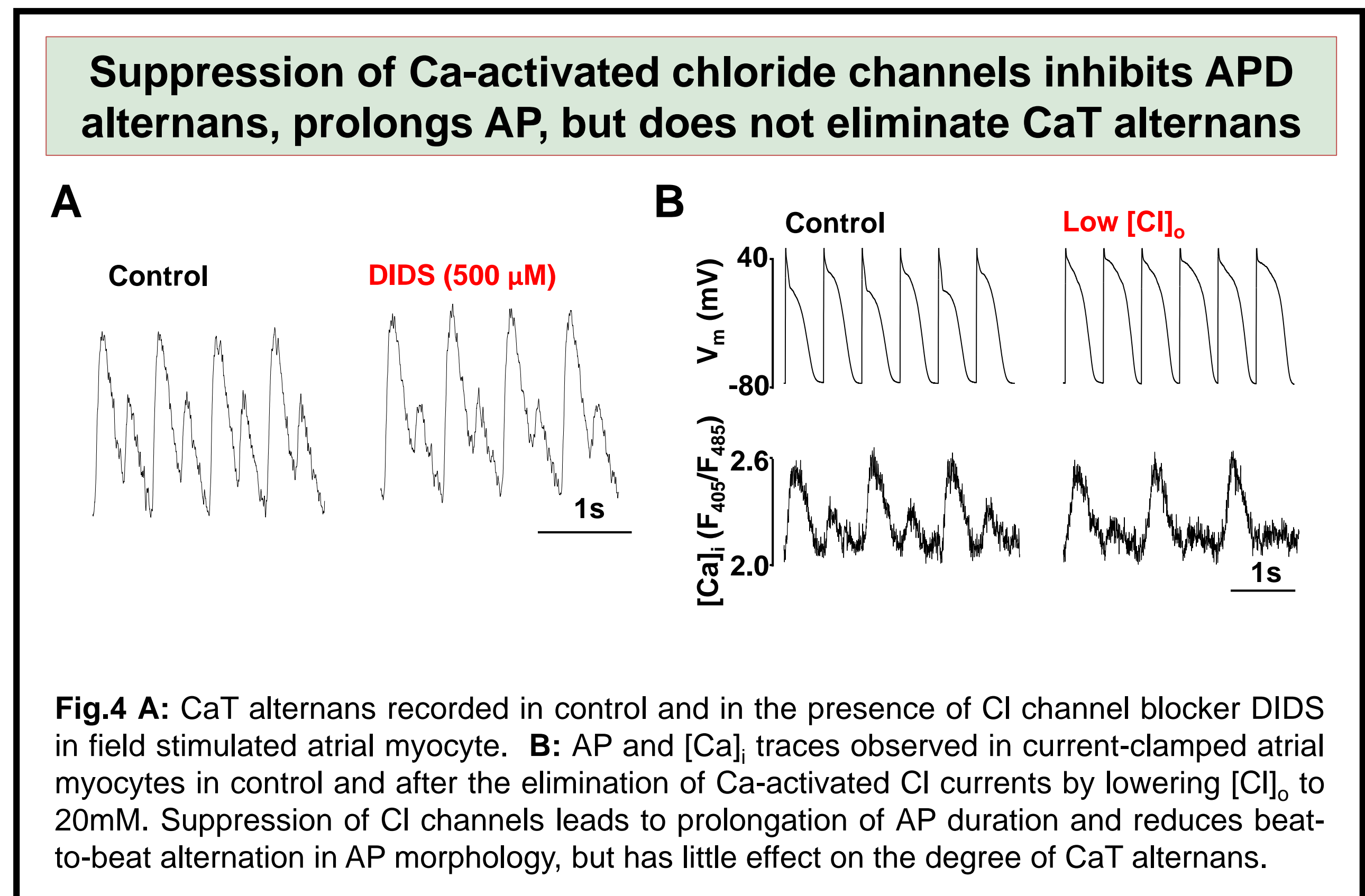
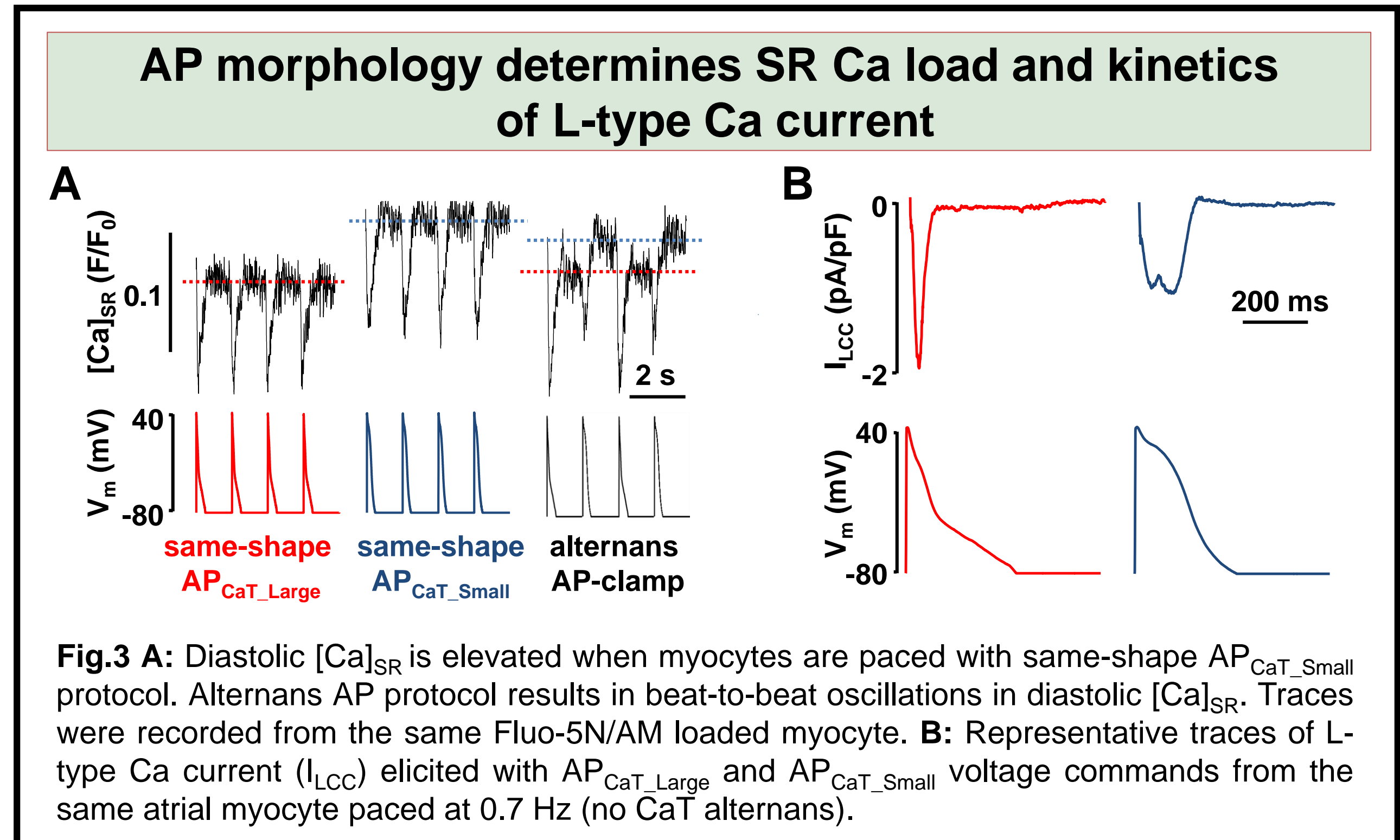
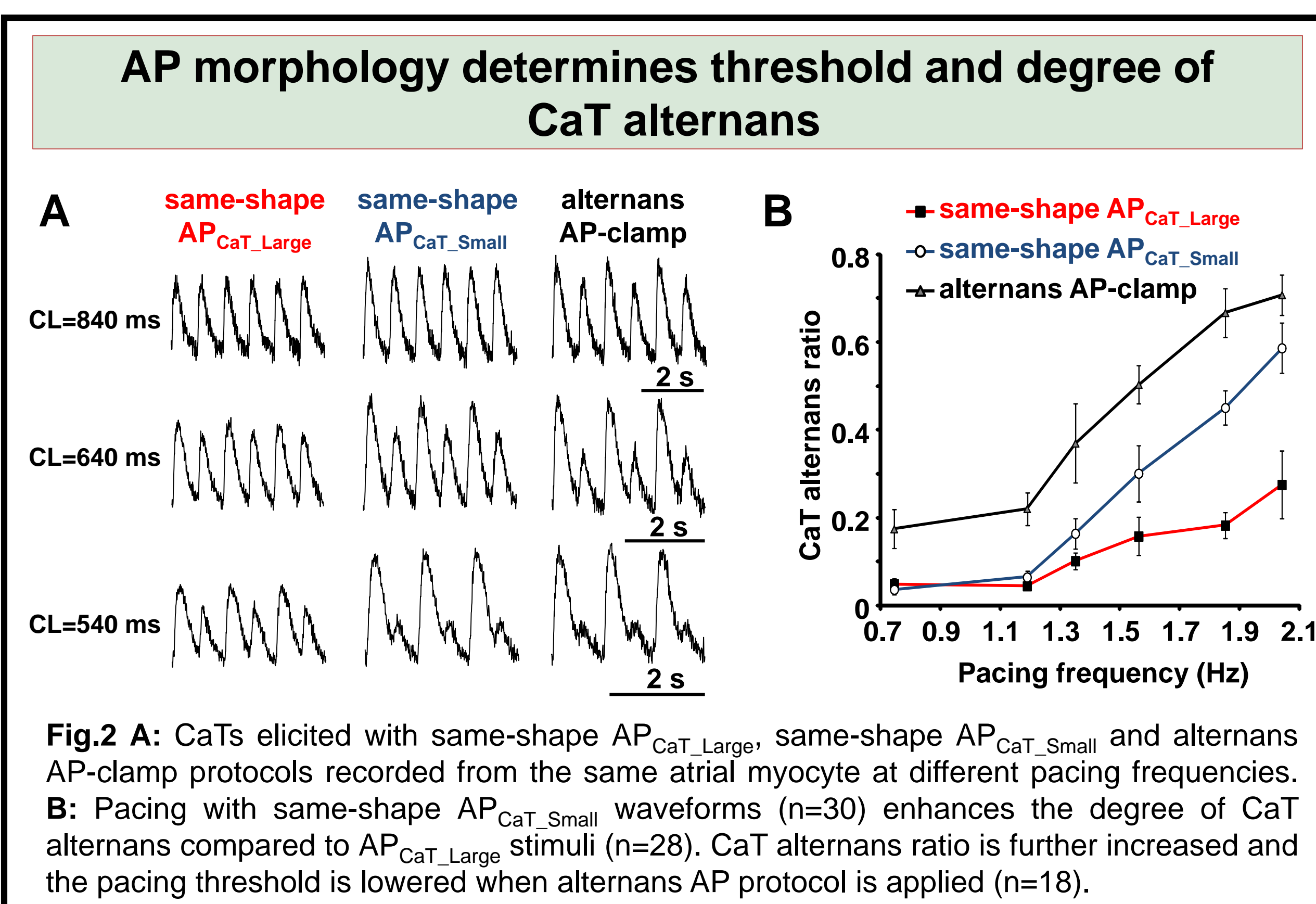


Introduction

Alternans is a risk factor for cardiac arrhythmia, including atrial fibrillation. At the cellular level alternans manifests as beat-to-beat alternations in contraction strength, action potential duration (APD) and magnitude of the Ca transient (CaT). Electromechanical and CaT alternans are highly correlated and interplay between membrane potential and intracellular Ca cycling plays a key role in the development and stability of cardiac alternans. In this study we demonstrate that severity of CaT alternans is strongly affected by the shape of APs and investigate if development of alternans can be prevented by targeted modulation of membrane ion channels that determine AP morphology. The findings that CaT alternans can be controlled or even prevented by pharmacological modulation AP morphology has important ramifications for arrhythmia prevention and anti-arrhythmic therapy strategies.

Methods

Experiments were performed on freshly isolated rabbit atrial cells. **Solutions:** External solution (in mM): 135 NaCl, 4 KCl, 2 CaCl₂, 1 MgCl₂, 10 D-glucose, 10 HEPES; pH 7.4 (NaOH). Patch pipette solution (in mM): 130 Kglutamate, 10 KCl, 10 NaCl, 10 HEPES, 0.33 MgCl₂, 4 MgATP; pH 7.3 (KOH). **Electrophysiological measurements.** Action potentials were recorded in current-clamp mode (Fig.1). These recorded APs were used as voltage commands in AP voltage-clamp experiments. **Fig.1 A:** Simultaneous recordings of AP and [Ca]_i alternans in current-clamped atrial myocytes. **B:** AP waveforms recorded during large (AP_{CaT, Large}) and small (AP_{CaT, Small}) alternans CaTs were used as voltage commands to pace cells during AP voltage clamp experiments. **C:** During AP-clamp experiments trains of voltage stimuli were applied as same-shape AP_{CaT, Large}, same-shape AP_{CaT, Small} and alternans AP stimulation protocols. **[Ca]_i measurements.** Simultaneously with electrophysiological recordings cytosolic [Ca]_i was recorded using Fluo-4 or Indo-1 pentapotassium salts (100 μM) added to the pipette solution. The degree of CaT alternans was quantified as the alternans ratio (AR), defined as AR=1-CaT_{Small}/CaT_{Large}, where CaT_{Small} and CaT_{Large} are amplitudes of small and large CaTs of an alternating pair of CaTs. **[Ca]_{SR} measurements** myocytes were loaded with the Ca probe Fluo-5N/AM entrapped in sarcoplasmic reticulum. All single cell experiments were performed at room temperature (22-24°C). **Whole heart.** Atrial electrograms were recorded by placing two electrodes on the left atria in Langendorf perfused isolated rabbit hearts. Electrical stimulation was applied to the right atria and stimulation frequency was gradually increased to induce atrial T-wave (T_a) alternans. Experiments were performed at 37°C. Statistical significance was evaluated using unpaired and paired Student's t-test and differences were considered significant at p < 0.05. Summarized data is presented as mean ± SEM.



Summary

- > Both disturbance of Ca signaling and AP dynamics play an important role in development of cardiac alternans
- > AP morphology contributes to CaT alternans by modulating: SR Ca load and kinetics of L-type Ca currents.
- > Occurrence and severity of CaT alternans can be modulated by pharmacological interventions targeting ion channels that shape the morphology of action potential: K channel agonists reduce APD and abolish CaT and APD alternans.

Acknowledgments

This study was supported by NIH grant awards HL057832, HL080101 and HL132871 to L.A. Blatter and AHA grant award 16GRNT30130011 to G. Kanaporis.