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Response to letter-to-editor by Dr. Karagueuzian

Madison S. Spach, M.D. and **Roger C. Barr, Ph.D.**
Duke University Durham, North Carolina

To the Editor – Response

Dr. Karagueuzian's comments on our article in the February in of Heart Rhythm,[1] are quite important and timely. In our cellular model studies of aging human atrial bundles we found that early premature stimuli delivered at the same site as the regular pacing stimulus produced initial decremental conduction that was spatially nonuniform, and this type of propagation led to incremental conduction that began in a small area, this small area also varying spatially with respect to the premature stimulus site. As pointed out by Dr. Karagueuzian,, we termed the small area where incremental conduction began to be a “conduction gate”. Because our model results reproduced the quite variable behavior that we found experimentally in human atrial bundles, and since the sodium current cannot be measured during propagation, we proceeded to use the detailed cellular model to look at the sodium current events that accounted (and/or accompanied) the complex conduction events within small areas near the premature stimulus site.

Using a two-stimulus (S_1-S_2) protocol that generates macroscopic repolarization gradients, the initial work of Chen[2] and Karagueuszian et al.[3,4] demonstrated that in uniform anisotropic ventricular muscle the initiation of propagation occurred between the S_1 and S_2 sites (away from the premature stimulus). Also, our results showed that with a single stimulus site without macroscopic repolarization gradients in aging atrial bundles early premature stimuli resulted in a “conduction gate” that was located away from the premature stimulus. We therefore suggested that their result “also appears to represent a “conduction gate”. In his letter, Dr. Karagueuszian importantly points out that, in their work, the timing of the premature stimulus occurred *earlier* than the “refractory period” before there was reactivation of sodium channels; i.e., typical graded responses in their studies, which occurred without lateral shifts in conduction, were generated from typical takeoff transmembrane voltages between −20 to −40 mV. This feature produces a different mechanism underlying the shift of the onset of propagation away from the premature stimulus site.

We were most pleased that Dr. Karagueuzian pointed out the difference in the premature responses in the different tissue types and with the different stimulus protocols. Because these features of early premature conduction represent a relatively unexplored area, his comments are especially important because they emphasize the need for more detailed experimental and modeling studies of the behavior of early premature stimuli in tissues of different ages and with different microstructures that have different patterns of cellular connectivity. For example, there are microstructural similarities in the nonuniform anisotropic pattern of cellular connectivity associated with microfibrosis in aging human atrial bundles and in the epicardial border zone that survives myocardial infarction. Specifically, Dr. Karagueuzian's notation is especially important that it will be of interest to determine if a “conduction gate” occurs with early premature stimuli in the ventricular border zone that survives infarction.

E-mail address: cspach@duke.edu

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