Microheterogeneity-induced conduction slowing and wavefront collisions affect macroscopic conduction behavior: a computational and experimental study

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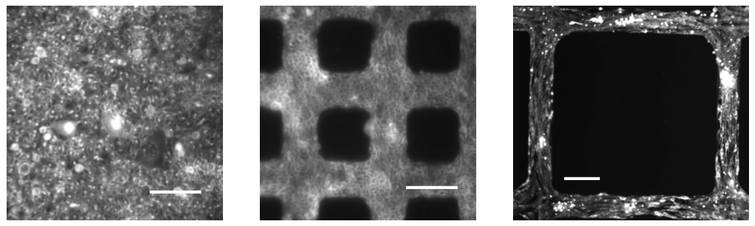
Introduction

Both experimental and clinical studies have shown that heterogeneity of the myocardium is strongly associated with arrhythmogenic behavior. However, the impact of structural microscopic heterogeneities on conduction is not well understood. The importance of cardiac microstructure in propagation and arrhythmogenesis was first described by Spach and colleagues. Several groups have examined how isolated microstructural heterogeneities affect local conduction and source-load balance, but it remains unclear how the aggregate behavior of numerous micro-heterogeneities affects macroscopic conduction, in part due to the inability to study conduction simultaneously on both the microscopic and macroscopic spatial scales. The objective of this study was to use paired experimental and computational studies of regular patterns of heterogeneity to understand how microscopic structural changes affect macroscopic conduction.

Methods

Monolayers with varying sizes of acellular, non-conductive heterogeneities were created by contact-transfer printing of fibronectin in the pattern of desired cell growth. Engineered excitable HEK293 cells (“Ex293”), which have simplified excitable machinery and can be directly modeled, were used. Resulting monolayers had density of nonconductive obstacles between 0% and 77%. Conduction behavior was recorded using optical mapping with a voltage sensitive dye. Palmitoleic acid (PA, 100 μM) was used to study the effects of reduced coupling.



Computational tissue models (dx,dy = 10 μm) were generated using each experimental tissue geometry. Cellular areas were considered homogenous. The previously described Ex293 membrane model was used. Conduction was simulated in Cardiowave using a semi-implicit Crank-Nicholson scheme with adaptive time steps between 10 μs and 2 ms. Virtual optical mapping was performed for direct comparison to experimental results.

Acknowledgements

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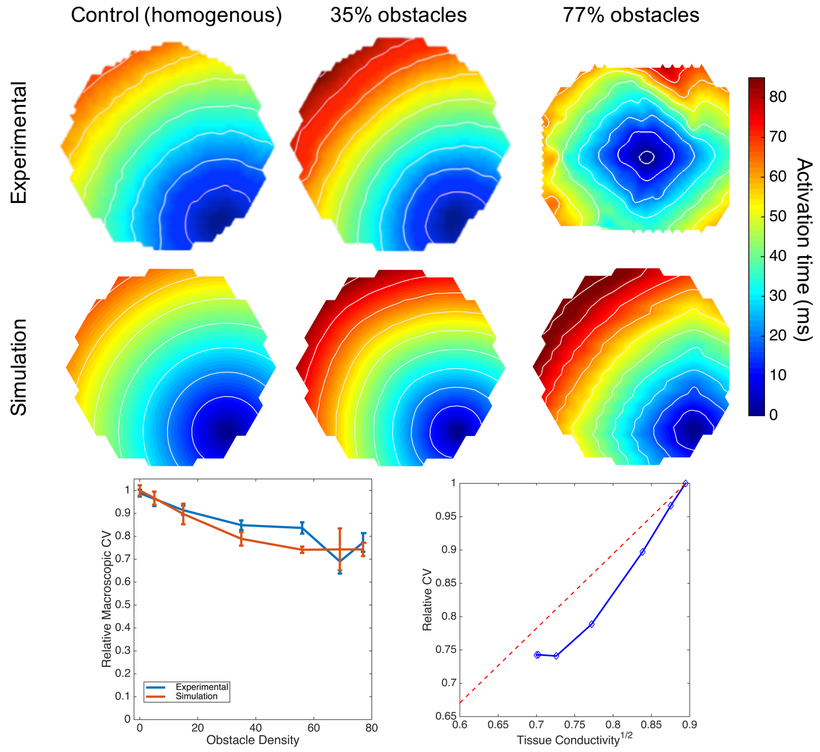
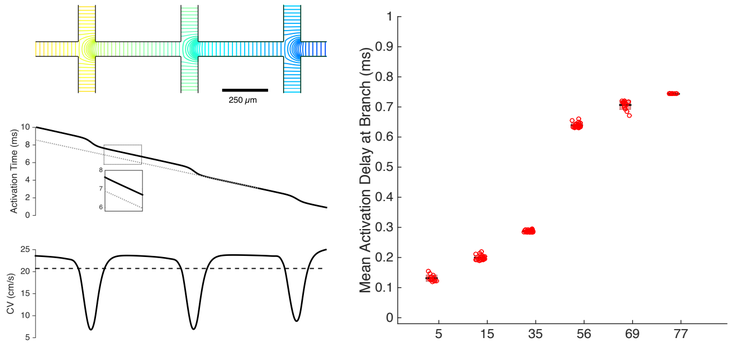
Results

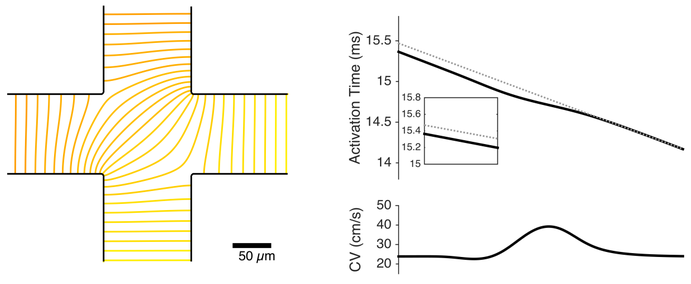
Increased heterogeneity leads to conduction velocity (CV) slowing in experimental and computational monolayers. Conduction becomes increasingly anisotropic in the presence of heterogeneity. Observed changes in CV cannot be explained by changes in tissue conductivity.



Examination of microscale conduction along the strands directly in line with the stimulus site showed substantial conduction slowing as the wavefront approached each branch point, with greater slowing at higher obstacle densities.

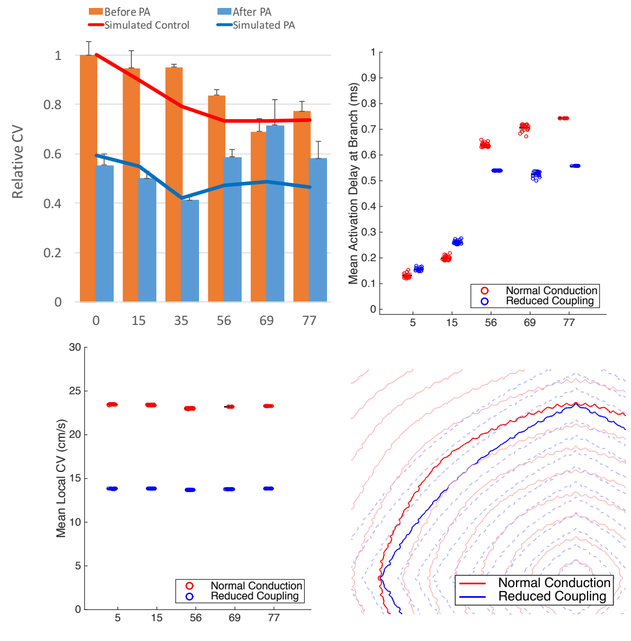


Along intersection points radially equidistant from the two primary axes, local speeding of conduction was observed due to collisions between two simultaneously arriving wavefronts. The activation acceleration due to these collisions is between 0 and 0.2 ms at each intersection point.

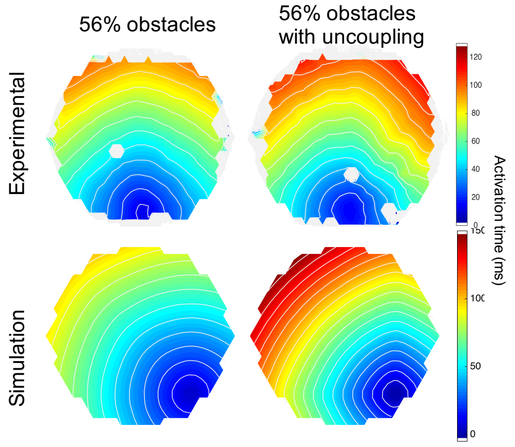


Results

The effect of reduced coupling was examined in the context of variable heterogeneity. Reduced coupling led to slowing of conduction, observed to be inversely related to obstacle density. This is attributed to reduced conduction delay at branch points in monolayers with higher obstacle density.



56% obstacles



Our work demonstrates that source-load mismatch-related slowing at branch points and wavefront collision-related acceleration at intersection points play a important and critical role in affecting macroscopic conduction, and that these forces are differentially modulated in the setting of reduced coupling.

References

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