Differences in healthy and unhealthy ventricles

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Background

Pathological remodeling in heart failure alters:

–3D tissue structure, cell geometry, cellular proteins and increases the expression of the collagen (fibrosis).

3D organization of myocardium influences electrical activity and arrhythmic substrates such as delayed and discontinuous activation are linked to ventricular fibrosis [1].

Aims

- Understand how structural features of diseased myocardium lead to delayed and discontinuous activation.

Method

- Collagen stained 3D volumes (Fig1) were imaged using high-resolution confocal microscopy.
- Images taken from left-ventricular freewall of 12 month old Wistar Kyoto (WKY) and Spontaneous hypertensive rat (SHR) rat models.
- WKY is healthy, while SHR is used to mimic heart failure [2].

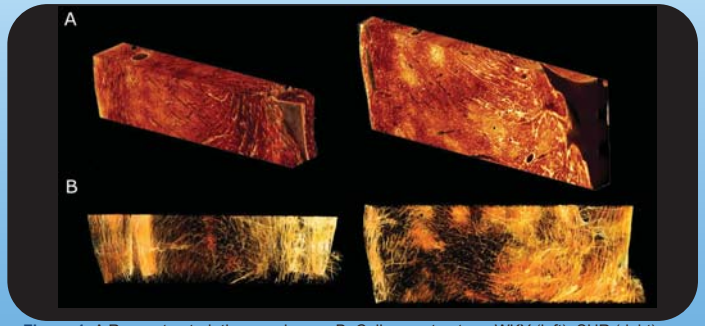

Figure 1: A Reconstructed tissue volumes. B. Collagen structure. WKY (left), SHR (right).

Method-comparison metrics

Connectivity and volume distributions

- Viable myocytes, collagen and extracellular space were differentiated on the basis of image intensity.
- Connectivity ➔ surface area of segmented myocytes in physical contact with neighboring myocytes.

Structural orientations

- The principal structural directions of the cardiac fibers were estimated using structural tensor analysis.

Activation Modelling

- Electrical activation was simulated through the tissue network description using a finite volume discretization of a monodomain reaction-diffusion model.

Results

Connectivity and volume distributions

- SHR tissue exhibits a larger collagen proportion per volume unit.
- WKY tissue is more connected compared to the SHR and shows a more symmetric distribution (Fig 2B).
- Connectivity reduction in SHR tissue is attributed to decreased lateral coupling from the increased volume of collagen.

Structural orientations

- SHR fiber angle diverges from WKY almost from the midwall (Fig 3). The collagen structure is strongly correlated with the fiber orientation.

Activation Modelling

- The coupling (and hence loading) differences between the WKY and SHR models is illustrated by the activation time (AT) sequences (Fig 4A).
- Both the conduction velocities (CV) and the action potential durations (APD) are similar for both models (Fig 4B,C).
- The CV distributions (Fig 4B) indicate that overall the CV is slower in the SHR model. Structural fibrosis is likely to act as a barrier for propagation.

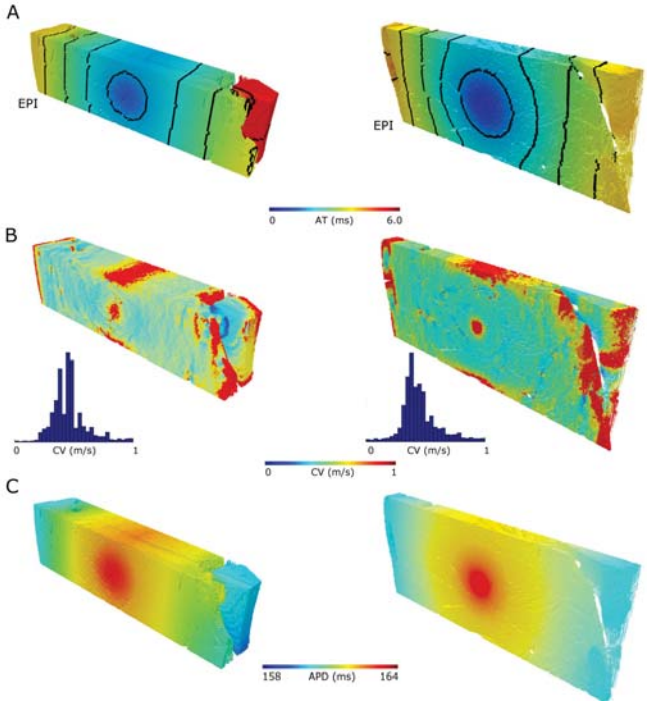

Figure 4 A. Activation. B. Conduction velocities : C. APD. WKY(Left), SHR(Right).

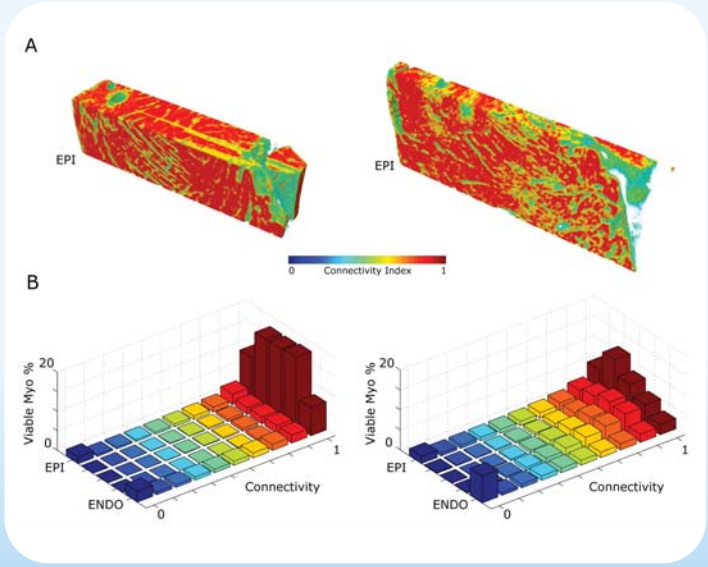

Figure 2 A. Tissue rendered with normalised connectivity. B. Frequency histograms of connectivity changes in subvolumes from epicardium and endocardium. WKY (left), SHR (right).

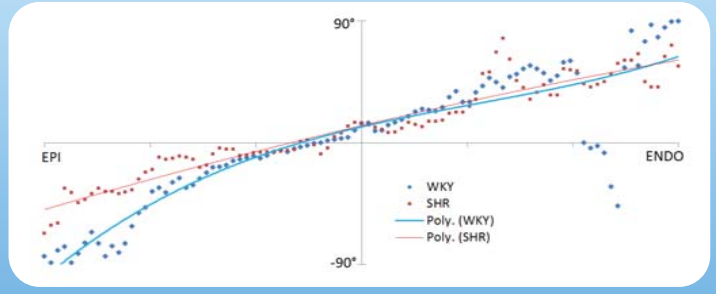

Figure 3 Fiber angle distribution from the epicardium and endocardium for WKY and SHR.

Conclusion

The preliminary data presented suggest that fibrosis in SHR tissue alters the electrical activity.

However exact mechanisms behind the differences are unclear. Cellular structural and functional modeling analysis is needed.

Future work

- Analyze multiple age matched tissue samples that are currently available.
- Integrate cellular level imaging with modeling presented here. Currently working on refining cellular imaging techniques.

References

1. Smaill, B.H., Zhao, J., Trew, M.L.: Three-dimensional impulse propagation in myocardium: arrhythmogenic mechanisms at the tissue level. Circ. Res. 112, 834–48 (2013).
2. LeGrice, I.J., Pope, A.J., Sands, G.B., Whalley, G., Doughty, R.N., Smaill, B.H.: Progression of myocardial remodeling and mechanical dysfunction in the spontaneously hypertensive rat. Am. J. Physiol. Heart Circ. Physiol. 303, H1353–65 (2012).