Progression of Atrial Electrical Dysfunction in Hypertensive Heart Disease

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Background

Hypertensive heart disease (HHD) is strongly associated with increased risk of atrial arrhythmia [1]. Although previous studies [2] have characterised differences in electrical behaviour between diseased and normal atria, a time-course study of the progression of HHD to failure in the atria has not been undertaken. In this study, we use the spontaneously hypertensive rat (SHR) model to elucidate the progression of electrical dysfunction over the course of HHD using **high resolution optical mapping**.

Materials & Methods

- Age-matched SHRs were studied at 6/7 months, 12/13 months and 18 months (n=6, n=8, n=6 respectively).
- High resolution optical mapping experiments (Figure 1) were performed on an isolated bi-atrial preparation, superfused with warm oxygenated Krebs-Henseleit solution. Blebbistatin (5 μM) was used for mechanical uncoupling and di-4-ANEPPS (10 μM) was used for membrane-voltage mapping.

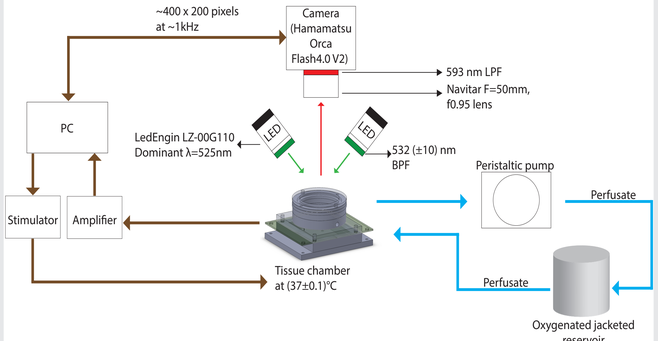

Figure 1: Schematic of experimental setup. The sample was placed in a tissue chamber with the epicardial surface facing the camera.

- Silver stimulus electrodes were introduced into the right and left appendages.
- Restitution kinetics were characterised using programmed S1-S1 stimulus over a range of intervals.
- Susceptibility to arrhythmia was assessed using a train of S1 pulses (250 ms intervals) followed by a single S2 pulse until loss of capture or induction of arrhythmia.
- Image processing involved the following steps: background fluorescence subtraction, spatial downsampling, spatial gaussian filtering, and temporal FIR low-pass filtering.

Results

Activation time (AT) maps during SR and stimulation (Fig 1) were consistent with previous studies [2,3], with activation spreading from the sino-atrial node and activation of the posterior left atrium (LA) via Bachmann's bundle. In 18-month old animals, however, we consistently observed **electrically quiescent patches** in the left atrial appendage (LAA) that markedly perturbed activation spread (Fig 2).

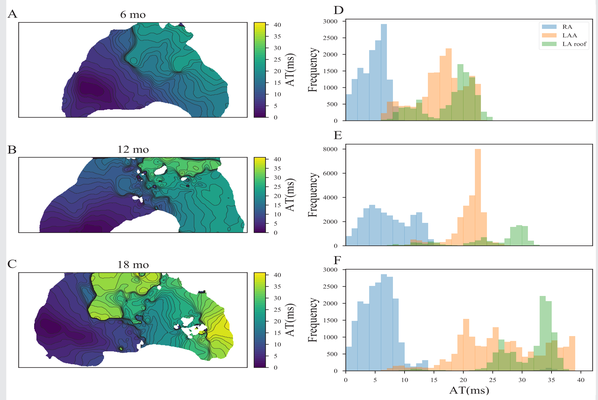

Figure 2: AT maps of representative A) 6 months old, B) 12 months old and C) 18 months old SHR paced from the RAA at 300ms interval. The histogram of regional AT distribution for each heart is shown in Figures D-F, demonstrating age dependent increase in activation delay.

An increase in action potential duration (APD) **heterogeneity**, especially in the LA was observed with age (Figure 3). APDs in the LA roof (LAR) were higher than APDs in the right atrium (RA) and LAA at all ages. Restitution slope in the LA was also steeper than the RA (Figure 4).

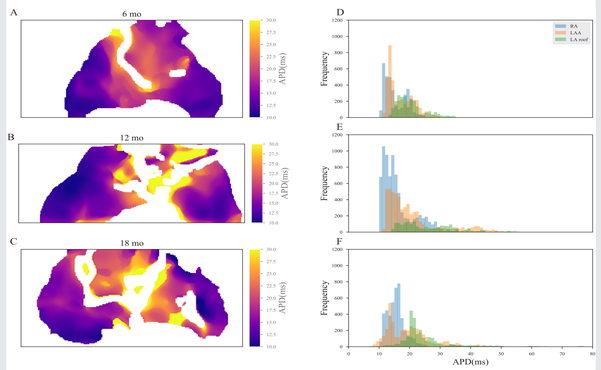

Figure 3: APD maps of representative A) 6 months old, B) 12 months old and C) 18 months old SHRs and the corresponding histograms of their regional distribution (D, E and F).

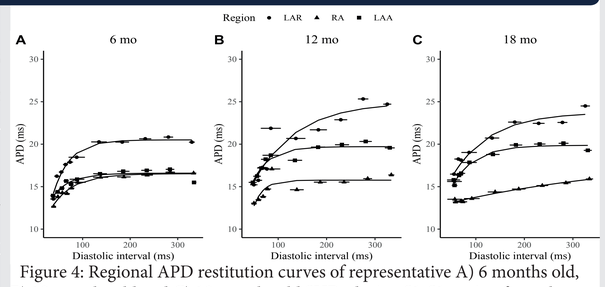

Figure 4: Regional APD restitution curves of representative A) 6 months old, B) 12 months old and C) 18 months old SHRs during S1-S1 pacing from the RAA. Note that mean values and standard error are shown here.

There was a rate and age dependent increase in **dispersion of repolarisation times** (Figure 5) between 6 months old animals and 12 and 18 months old animals ($p<0.00001$). There was a significant increase in low voltage regions with age (Figure 6).

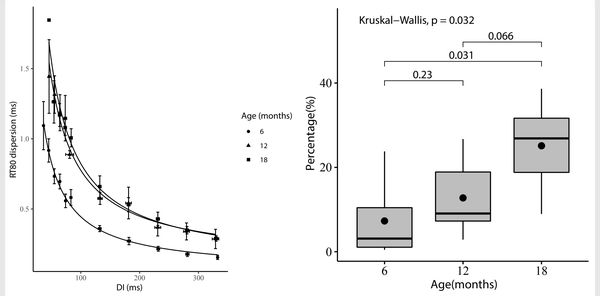

Figure 5: Variation of dispersion of repolarisation with age and pacing interval. Mean and standard deviation values are shown for each data point.

Figure 6: Area occupied by inactive (low voltage) regions as a percentage of the total LAA area for each age group.

There was a significant reduction in **global conduction velocities** (both RA-to-LA and LA-to-RA) with age (6 months old and 12/18 months old). However, the difference between the 12 months old group and 18 months old group was not significant.

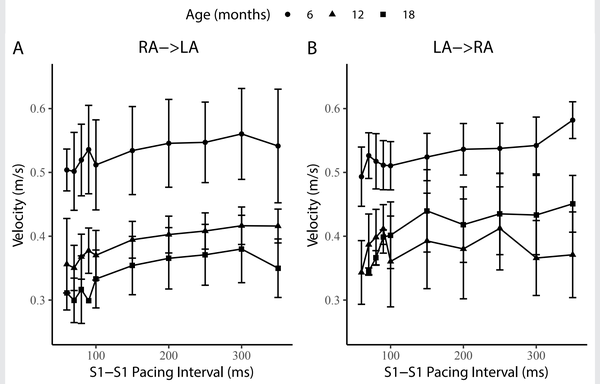

Figure 7: Variation of conduction velocities with S1-S1 pacing for A) right-to-left and B) left-to-right conduction for each age group.

Susceptibility to arrhythmia increased with age. The **frequency of sustained macro-reentrant pathways** (Figure 8A), as well as the **frequency of reentrant drivers** (Figure 8B) decreased with age. Older animals were also more vulnerable to macro-rentry as compared to younger animals (Figure 9).

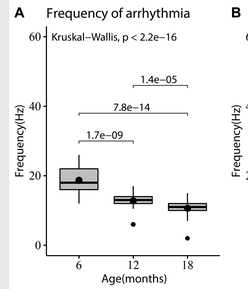

Figure 8: A) Frequency of sustained macro-reentry at 6, 12 and 18 months. B) Frequency of re-entrant drivers at 6, 12 and 18 months.

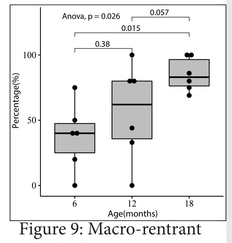

Figure 9: Macro-rentrant arrhythmia as a percentage of total number of events of arrhythmia.

Reentry was most commonly initiated from the LAR (Figure 10), which correlated with a longer total activation (Figure 11) or refractoriness of the region.

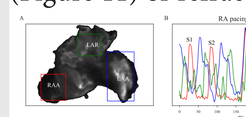

Figure 10: Activation of the RAA, LAA and LAR during S1-S1 pacing from the RAA.

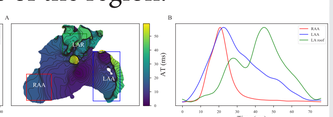

Figure 11: A)Activation map and B) regional activation of the RAA, LAA and LAR at initiation of reentry.

Discussion & Conclusion

Our results demonstrate that the progression of HHD is accompanied by a deterioration of electrical conduction in the atria, which increased the susceptibility to arrhythmia. These include:

» Increase in activation delay in the LA
» Increase in APD heterogeneity in the LA
» Increase in dispersion of repolarisation times
» Decrease in conduction velocity
» Increase in area of inactive tissue

Electrical dysfunction was **more pronounced in the LA than the RA**. These results strongly suggest that structural remodelling in the LA is a key contributor to susceptibility to atrial arrhythmia in HHD.

References

[1] Burstein B. & Nattel, S. J Am Coll of Cardiology 20008; 51:802-809.
[2] Lau, D. H. et al. PLoS ONE.2013;8(8).
[3] Nygren, A. et al. Am J of Physiology 2004; 287; 6:2634-2643