

## Development of the sinoatrial and atrioventricular nodes in the avian embryo: a reference series of morphological and electrophysiological changes during maturation

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**Objectives:** Analysis of the morphological and electrophysiological development of the sinoatrial (SAN) and atrioventricular (AVN) nodal areas can help us to unravel the mechanisms behind specific arrhythmias. In this study we provide an overview of the morphological changes that occur in SAN and AVN differentiation during avian heart development, and provide baseline measurements of developmental changes in the electrograms.

**Methods:** The developing SAN and AVN area were studied for expression patterns of the cardiac markers cTnI, Nkx2.5, the gap junction protein Cx43 and the cation channel HCN4. The developing electrogram was studied by *ex ovo* local electrophysiological recordings as well as atrial activation patterns.

**Results:** Initially, the entire sinus venosus myocardium expresses cTnI, HCN4, but not Nkx2.5, and has the potential to generate the first electrical activity resembling a pacemaker. At later stages both expression patterns and electrical activation patterns become restricted to the definitive right sided SAN. Similarly, the early atrioventricular canal and at later stages the atrioventricular ring myocardium and AVN areas show a common expression pattern. During development we observed a significant increase in heart rate and atrioventricular delay (Figure). Lineage tracing experiments show a potential sinoatrial contribution to the AVN area.

**Conclusions:** Significant changes occur in both morphology and electrical properties of chick sinus venosus and atrioventricular ring myocardium during development, where the putative SAN and AVN will form, respectively. The broad electrical potential of these structures during development may form an explanation for the occurrence of predilection sites for arrhythmias in the adult.

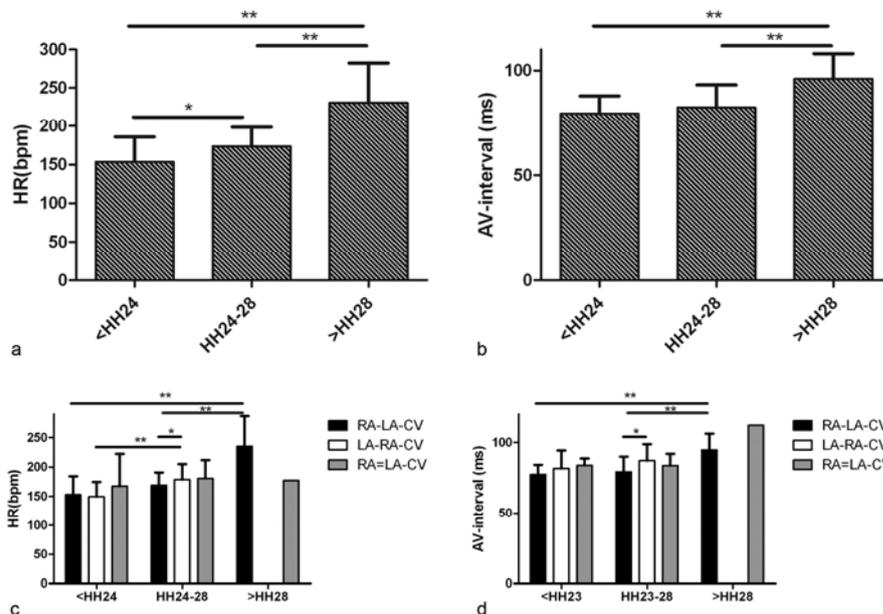


Figure. Electrophysiological changes during development. a-b show the changes in heart rate (HR) in beats per minute (bpm)(a) and atrioventricular (AV) interval in milliseconds (ms)(b) during development. c-d show the changes in HR and AV interval during development for the different atrial activation patterns. RA-LA-CV: right-sided dominant pacemaker; LA-RA-CV: left-sided dominant pacemaker; RA=LA-CV: concurrent activation. \*:p<0.05; \*\*:p<0.005.