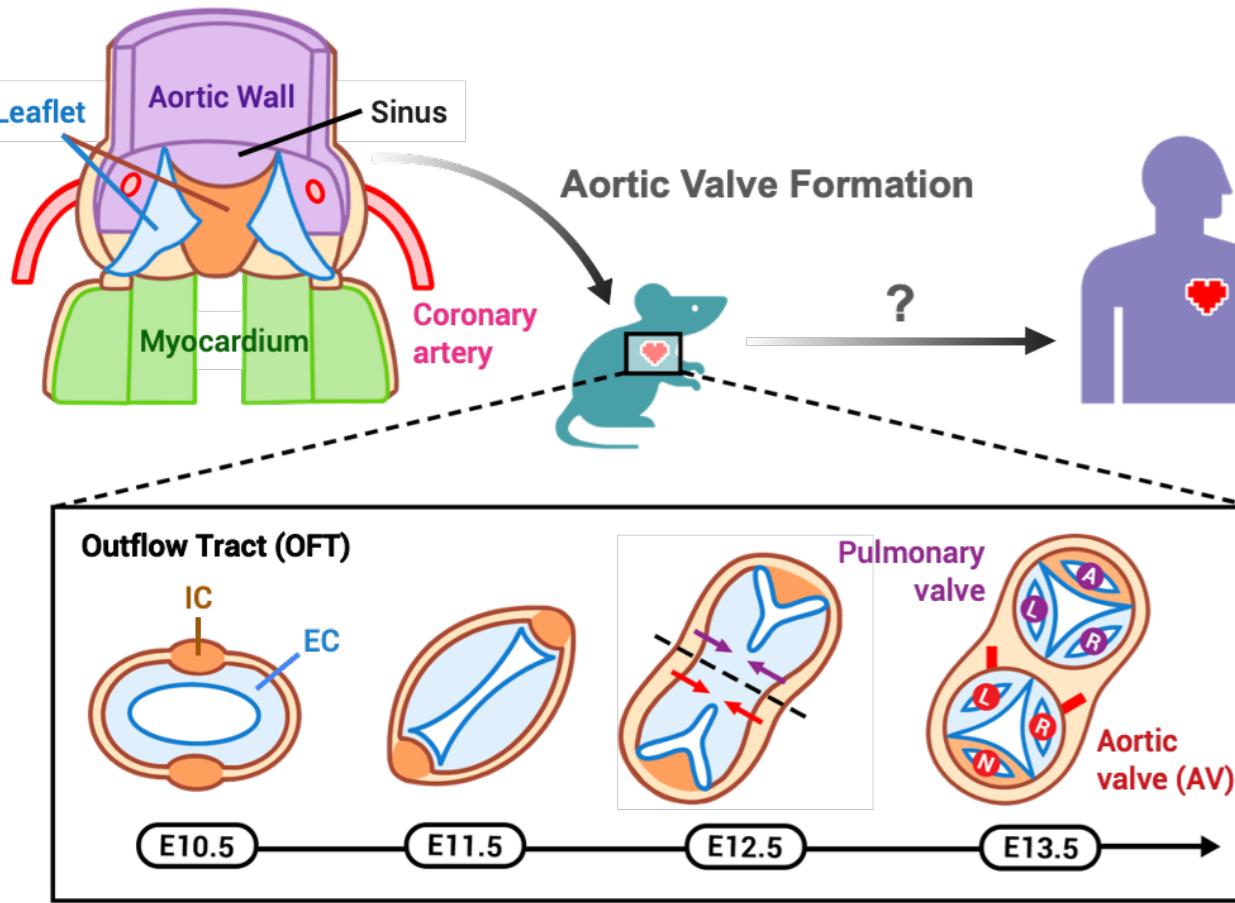


Aortic Valve Development and Remodeling in the Human Embryo

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INTRODUCTION



The formation of AV has been extensively studied in mice, but is it the same in human?

A, anterior leaflet; EC, endocardial cushion; IC, intercalated cushion; L, left leaflet; N, non-coronary leaflet; R, right leaflet; S, sinus

- AV is vital to keep unidirectional blood flow to the whole body, but it is **common to be congenitally malformed**.
- **Bicuspid AV** is the most prevalent (1-2% of all population) and has **late complications** (AV stenosis, heart failure).¹
- AV anomalies are studied by looking at the **basic AV development in mouse models** in hopes of replicating the process in human.²
- Without knowing **how human AV normally develops**, it is hard to say that the mechanisms found in mouse are relevant to congenital valve malformations in human.

HYPOTHESIS

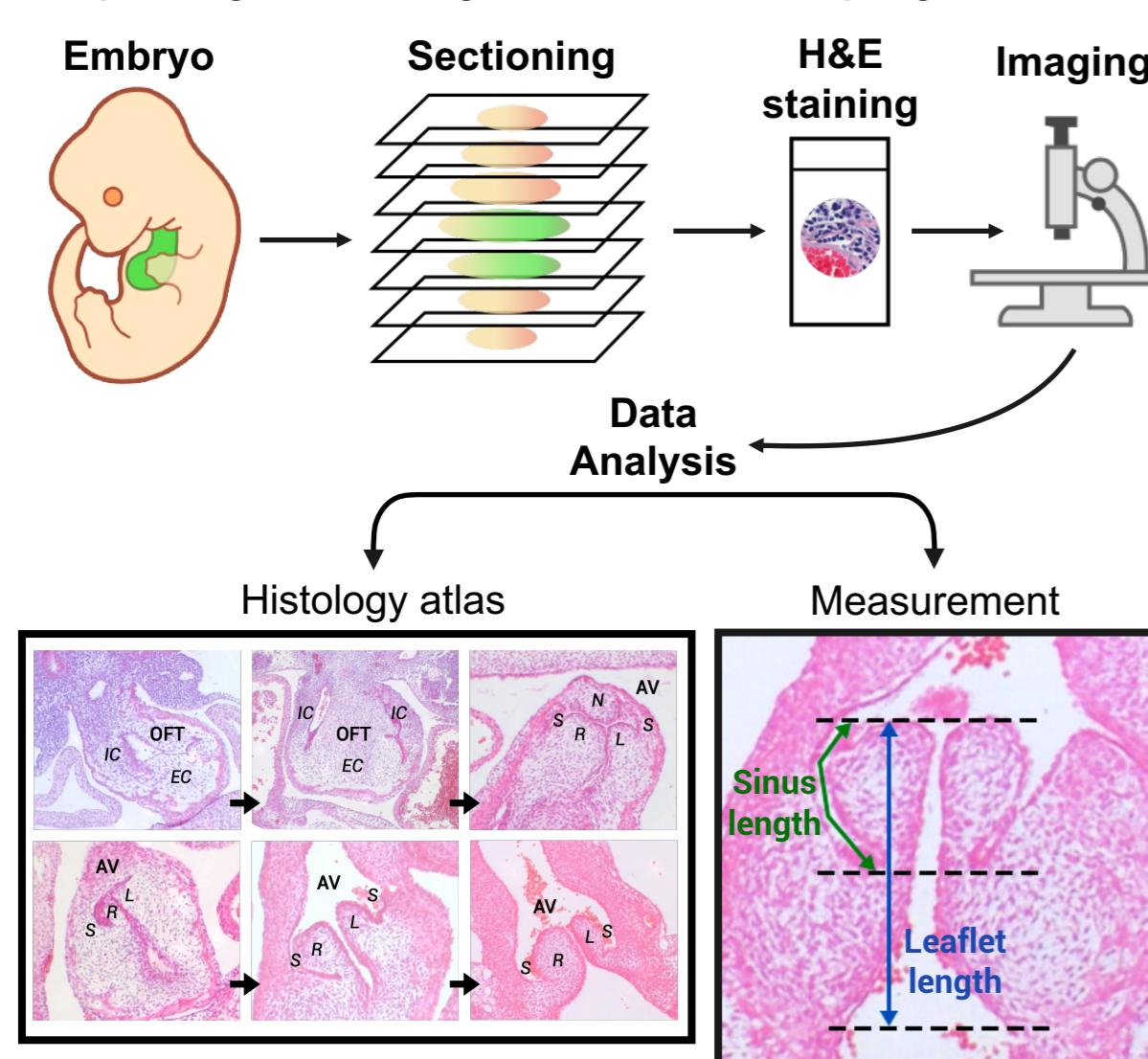
AV development and remodeling is the same between mouse and human embryos.

OBJECTIVES

- Record both **morphological events** and **timeline** of AV development in human embryos
- Measure **leaflet and sinus length** in human embryos
- Perform **comparative analysis** to mouse embryos

METHODOLOGY

H&E staining is used to visualise the key structures and morphological changes of the developing aortic valve.



Histological sections in transverse orientation were provided by the HDBR³ [15 human: CS14 (n=3), CS16 (n=4), CS17 (n=1), CS18 (n=1), CS19 (n=3), CS22 (n=3)] and Henderson/Chaudry lab⁴ [CD1 mice: E11.5-18.5].

Measurement was done in ImageJ. Statistical analyses were done in SPSS.

CONCLUSION

- Morphological features of AV are comparable, indicating both species follow the **same sequence of events**
- Timing for leaflets maturation is longer in human, suggesting **bulky leaflets are sufficient** to maintain the unidirectional blood flow during fetal period
- Human AV remodels via **sinus excavation** as previously described in mouse embryos⁵
- **Mouse is a good model** to study human valvulogenesis.

RESULTS

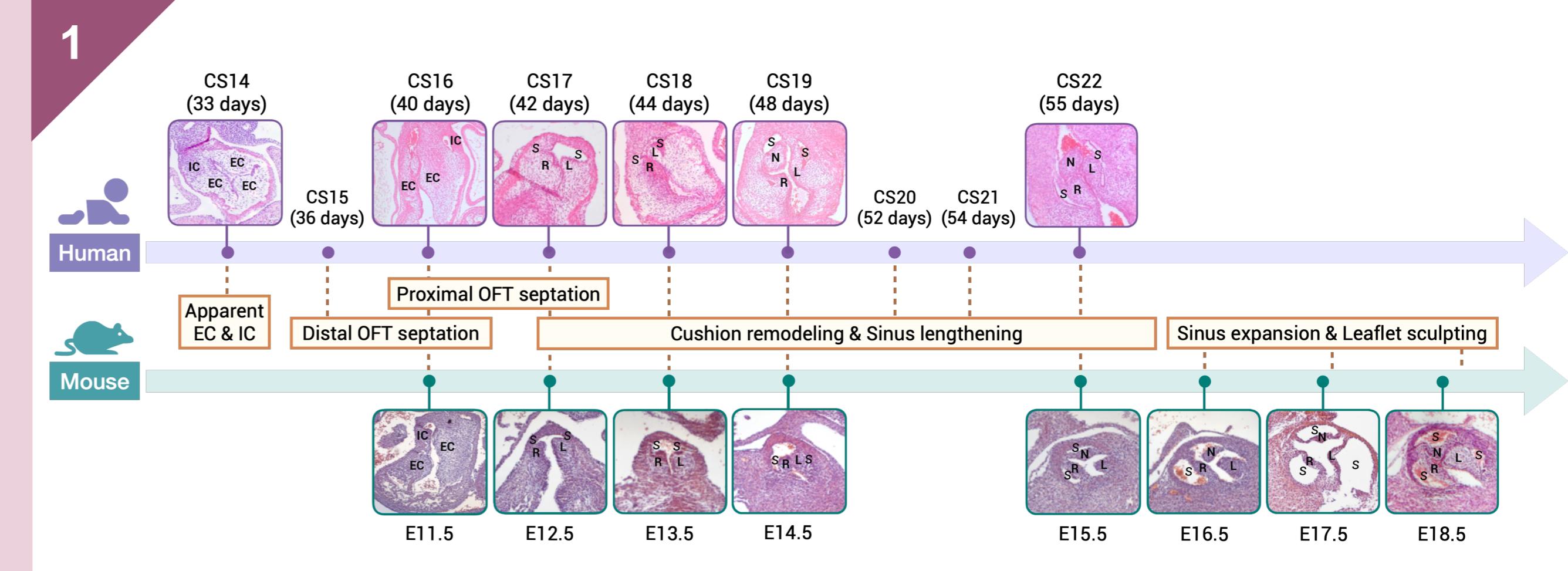


Fig. 1 Human AV appears and forms similar to mouse but matures slower

Top panel presents the H&E sections of human embryos from Carnegie stage (CS)14-22. Middle panel details the morphological events occurred in human, mouse or both (dashed line). Bottom panel shows those of mouse embryos from embryonic day (E)11.5-18.5.

- In the **early phase**, the appearance of OFT and AV **changed sequentially** between human and mouse
- After the **OFT has been completely separated**, the subsequent process **slowed down in human**.
- It is apparent that **mouse AV matured remarkably faster** just before birth, compared to human at the end of the observation when the leaflets were still short and thick.

2

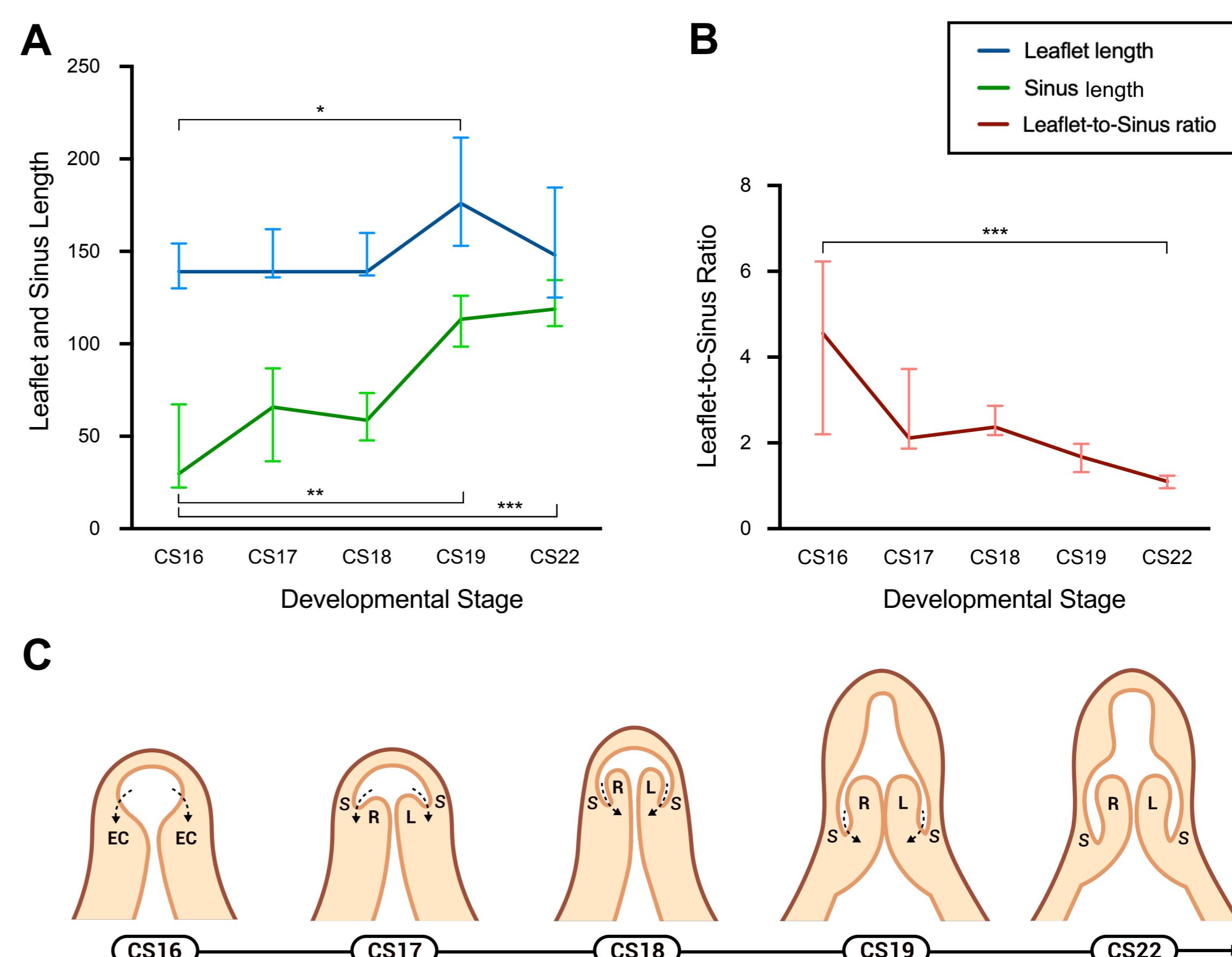


Fig. 2 Remodeling of human aortic valve is dependent on sinus excavation

Leaflet and sinus length were measured using 3 representative sections from 1 or 3 different embryos at CS16-22 [CS16 (n=9), CS17 (n=3), CS18 (n=3), CS19 (n=9), CS22 (n=9)]. These were summarised into leaflet-to-sinus ratio to determine whether cushions remodel through leaflet outgrowth or sinus ingrowth. Statistical analyses were presented as median (interquartile range) and performed using Kruskal-Wallis test with Dunn-Bonferroni test to compare the changes of leaflet length, sinus length and leaflet-to-sinus ratio in CS16-22 (*p<0.05; **p<0.01; ***p<0.001).

(A) Leaflet length did **not** relatively change, whereas sinuses exponentially grew deeper.

(B) These measurements were summarised into **leaflet-to-sinus ratio** which significantly declined as the embryos age, supporting the concept of **sinus excavation** as to how cushions remodel into thin leaflets (C).

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