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Excessive trabeculations in noncompaction do not have the embryonic identity

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ABSTRACT

Background: Ventricular noncompaction is characterized by excessive trabeculations and is associated with heart failure. The lesion is hypothesized to result from failed compaction and thus retention of embryonic trabeculations. Here, we assess for the first time the identity of trabeculations in noncompaction to test whether noncompacted hearts show retention of embryonic trabeculations.
Methods: Using immunohistochemistry, we analyzed cardiac sections of the heart of a control embryo, 3 cases of fetal noncompaction (a set of twins and an unrelated fetus) and 3 fetal hearts without noncompaction.
Results: In the embryo, the ventricular trabeculations strongly expressed ANF/NPPA whereas the compact wall did not. In the noncompaction hearts, trabeculations constituted an excessively thick layer. In noncompaction and control fetal hearts alike, however, only a miniscule subset of sub-endocardial myocardium of the trabeculations most proximal to the central ventricular lumen exhibited strong expression of ANF/NPPA, representing Purkinje myocardium. The trabeculations of both fetal control and noncompaction hearts were ANF-negative and orders of magnitude wider than those of the embryo. Both the compact and noncompaction trabeculated myocardium were rich in coronary vasculature. Like embryonic trabeculations, the ANF^{+} Purkinje myocardium had little if any vasculature.
Conclusion: The excessive trabeculations in noncompaction do not have the embryonic identity and noncompaction is probably not the result of failed compaction. We propose the lesion results from the compact wall growing into the ventricular lumen in a trabecular fashion.

1. Introduction

Left ventricular noncompaction or hypertrabeculation is a cardiomyopathy characterized by excessive trabeculations and is associated with a high risk of heart failure and sudden cardiac death [1,2]. The lesion is thought to result from failed compaction of the embryonic trabeculations, whereby an excessive amount of trabeculations linger in the ventricular lumen [1].

Heart development sees the formation of a looped heart tube. Chambers grow at the outer curvatures of the looped heart tube and the expanding ventricles start to acquire trabeculations from around week 4 [3]. Within days, trabeculations become the bulk of the ventricular myocardium, giving the ventricles a 'spongy' appearance. Mouse studies show the trabeculations grow by proliferation at their base at the connection with the compact wall, which at this point is only a few cell layers thick [4]. The embryonic trabeculations are less than 50 μm wide, only a few cells across, without coronary vasculature, and rich in ANF/*NPPA* and CX40/*GJA5* [3,5]. By gestational week 6 in human, the trabeculations have effectively ceased to proliferate, whereas the compact walls continue to grow, by which the ventricles expand exteriorly and a ventricular lumen develops [3,6]. The embryonically formed trabeculations will therefore constitute a progressively smaller part of the ventricular myocardial mass during the fetal period. Meanwhile they maintain the ANF and CX40 positive phenotype and will eventually give rise to the Purkinje network of the conduction system [7–9].

Here we compare normal and noncompacted fetal human hearts and show the Purkinje myocardium is not excessive in noncompaction. This finding is surprising if one expects noncompaction to develop from excessive embryonic trabeculations, but is not surprising given mouse models of noncompaction [10,11] showing the compact wall growing into the ventricular lumen in a trabecular fashion.

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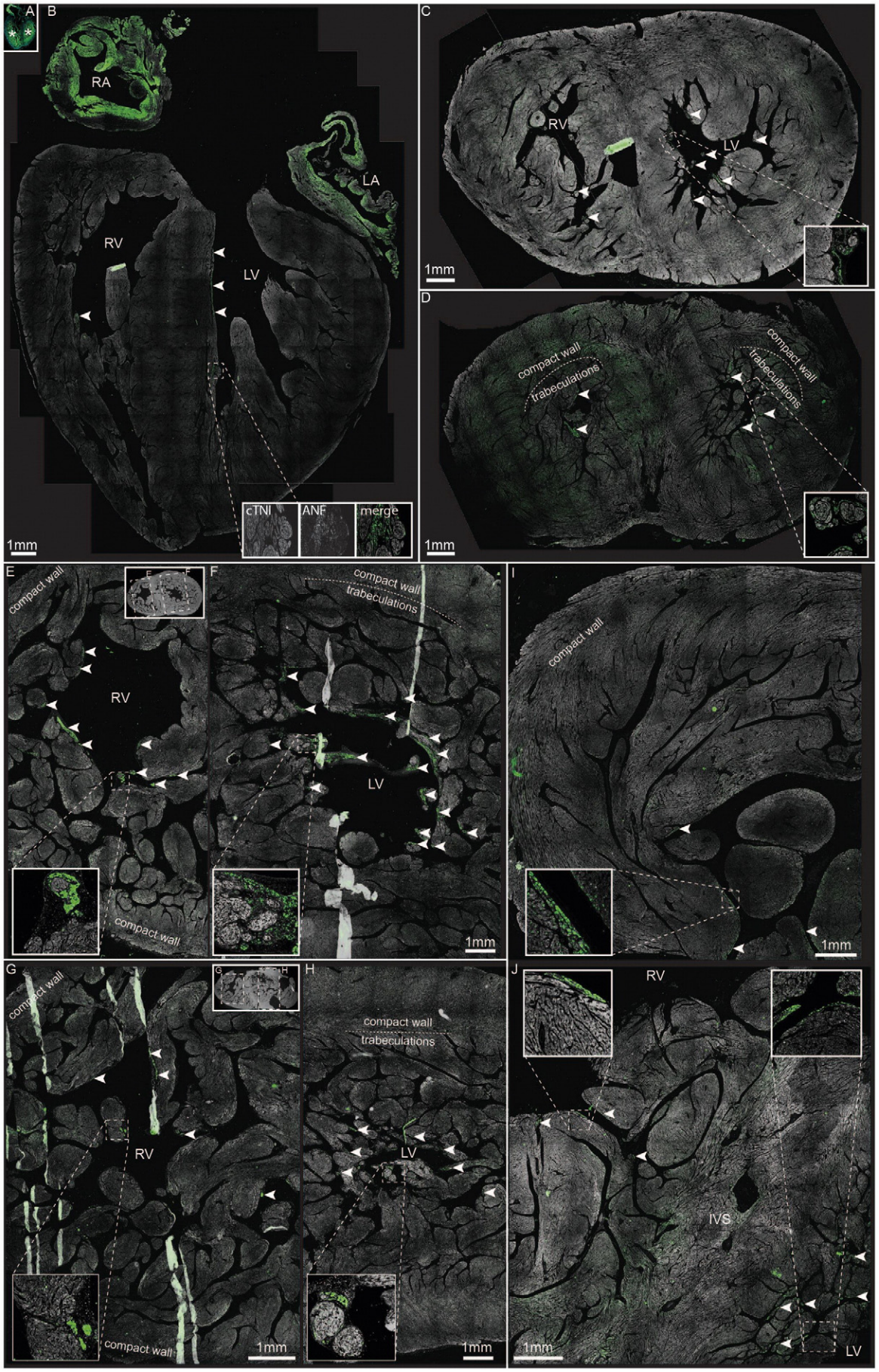
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