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Left ventricular non-compaction (LVNC), characterized by hypertrabeculation and deep trabecular recesses in the left ventricle, is the most common cardiomyopathy with a spectrum ranging from extreme normal variants to a pathological phenotype. In all forms, heart failure and sudden cardiac death represent the most severe complications related with non-compaction and arrhythmias. Defects in ventricular compaction and conduction are traits observed in patients and mutant mice carrying mutations in NKX2-5, encoding a key transcriptional regulator of cardiac development. In order to dissect the role of this gene in the apparition of the pathological outcomes of LVNC, we established a LVNC mouse model by inactivating Nkx2-5 in a time and tissue specific manner. Nkx2-5 was conditionally knockout in atria and trabecular cardiomyocytes at embryonic stages, when trabeculae arise, or during fetal stage, when they start to compact, or at neonatal stages, when the ventricles are mature. Our results show that the loss of Nkx2-5 at embryonic stages provokes a hypertrabeculation associated with important subendocardial fibrosis and Purkinje fibers hypoplasia in adult mice. These phenotypes are milder when the deletion occurred at fetal stages. Deletion only in the ventricular conduction system, at neonatal stage, leads to a progressive hypoplasia of this tissue without signs of hypertrabeculation nor fibrosis. However, all these mice develop progressively conduction defects and heart failure. The analysis of molecular pathways associated to these phenotypes, demonstrated that Nkx2-5 plays pleiotropic roles during trabecular development. Thus, deletion of Nkx2-5 during trabecular development represents a good model for studying the cellular and molecular mechanisms associated with LVNC, and the more pronounced disorder is provoked by a deletion at earlier stages.