Connexin45 contributes to global cardiovascular development by establishing myocardial impulse propagation

Abstract

Among gap junction-encoding genes, the loss of connexin (Cx) 45 most profoundly obstructs embryogenesis through an endocardial cushion defect and conduction block. However, the interdependence of these defects is not known, and the details of conduction block have not been elucidated. Here, we examined mouse embryos with a region-specific deletion of Cx45 in the myocardium (CA-Cre; Cx45(flox/flox)) or endothelium (Tie2-Cre; Cx45(flox/flox)). Although the deletion of Cx45 in the myocardium was heterogeneous, the CA-Cre; Cx45(flox/flox) embryos were lethal at the same stage as the constitutive Cx45-deficient (Cx45(-/-)) embryos. We determined the onset and patterns of their conduction block through point-tracking in video recordings of embryonic heart contractions. An incomplete conduction block at the atrioventricular canal appeared at embryonic day (E) 8.5 and was predominant around the lethal E9.5 stage in both the Cx45(-/-) and CA-Cre; Cx45(flox/flox) embryos. Although the Cx45(-/-) hearts showed a consistently severe reduction in atrioventricular conduction velocity, the CA-Cre; Cx45(flox/flox) hearts had delay times within the normal range and showed frequent retrograde conduction. As previously reported, the Cx45(-/-) endocardial cushion was consistently defective, and nuclear factor of activated T-cells cytoplasmic (NFATc)1 within the endocardium showed inactive cytoplasmic distribution. In CA-Cre; Cx45(flox/flox), however, the endocardial cushion was partially formed, with active NFATc1 within the endocardium. There was no developmental abnormality in the Tie2-Cre; Cx45(flox/flox) embryos. These results indicate that myocardial dysfunction is responsible for most of the reported defects in Cx45(-/-), which are alleviated by sporadic Cx45 expression in the CA-Cre; Cx45(flox/flox) myocardium.